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**APPLICATION NUMBER: 60/552,690**

**FILING DATE: *March 12, 2004***

**RELATED PCT APPLICATION NUMBER: *PCT/US05/07867***



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**PROVISIONAL APPLICATION FOR PATENT COVER SHEET**

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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**INVENTOR(S)**

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Additional inventors are being named on the \_\_\_\_\_ one \_\_\_\_\_ separately numbered sheets attached hereto

**TITLE OF THE INVENTION (500 characters max)****ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**Direct all correspondence to: **CORRESPONDENCE ADDRESS**☒ Customer Number:

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**ENCLOSED APPLICATION PARTS (check all that apply)**☒ Specification Number of Pages 79☐ CD(s), Number \_\_\_\_\_☐ Drawing(s) Number of Sheets \_\_\_\_\_☒ Other (specify) RETURN POSTCARD☒ Application Data Sheet. See 37 CFR 1.76**METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT**☐ Applicant claims small entity status. See 37 CFR 1.27.☐ A check or money order is enclosed to cover the filing fees.☐ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: \_\_\_\_\_☐ Payment by credit card. Form PTO-2038 is attached.FILING FEE  
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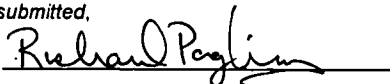
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.☐ Yes, the name of the U.S. Government agency and the Government contract number are: \_\_\_\_\_

[Page 1 of 2]

Respectfully submitted,

SIGNATURE



TYPED or PRINTED NAME Richard H. Pagliery

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Date March 12, 2004

REGISTRATION NO. 44,276

(if appropriate)

Docket Number: 45026.00153.PRV

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**PROVISIONAL APPLICATION COVER SHEET**  
**Additional Page**

PTO/SB/16 (08-03)

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Docket Number 45026.00153.PR.V

INVENTOR(S)/APPLICANT(S)		
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Number 2 of 2

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PROVISIONAL APPLICATION  
UNDER 37 CFR § 1.53(C)

TITLE:                   **ANDROGEN RECEPTOR MODULATOR COMPOUNDS  
AND METHODS**

APPLICANTS:       Lin Zhi, Robert I. Higuchi  
                          and E. Adam Kallel

Correspondence Enclosed:

Provisional Application Cover Sheet (1 pg);  
Provisional Application for Patent Cover  
Sheet (PTO/SB/16 – 2 pgs); Specification  
(67 pgs); Claims (11 pgs); Abstract (1 pg);  
and Return Postcard.

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## ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

### Background of the Invention

#### Field of the Invention

[001] This invention relates to compounds that bind to androgen receptors and/or modulate activity of androgen receptors, and to methods for making and using such compounds.

#### Background

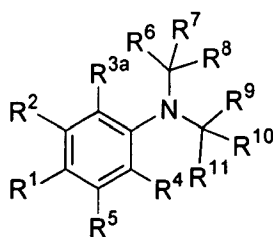
[002] Certain intracellular receptors (IRs) have been shown to regulate transcription of certain genes. *See e.g.*, R. M. Evans, *Science*, 240, 889 (1988). Certain of such IRs are steroid receptors, such as androgen receptors, glucocorticoid receptors, estrogen receptors, mineralocorticoid receptors, and progesterone receptors. Gene regulation by such receptors typically involves binding of an IR by a ligand.

[003] In certain instances, a ligand binds to an IR, forming a receptor/ligand complex. Such a receptor/ligand complex may then translocate to the nucleus of a cell, where it may bind to the DNA of one or more gene regulatory regions. Once bound to the DNA of a particular gene regulatory region, a receptor/ligand complex may modulate the production of the protein encoded by that particular gene. In certain instances, an androgen receptor/ligand complex regulates expression of certain proteins. In certain instances, an androgen receptor/ligand complex may interact directly with the DNA of a particular gene regulatory region. In certain instances, an androgen

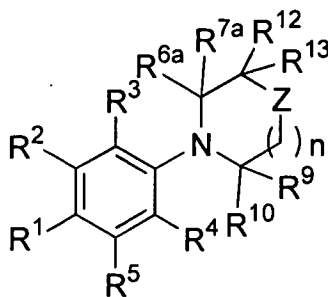
receptor/ligand complex may interact with other transcription factors, such as activator protein-1 (AP-1) or nuclear factor  $\kappa$ B (NF $\kappa$ B). In certain instances, such interactions result in modulation of transcriptional activation.

Summary of the Invention

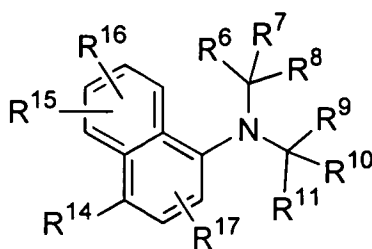
[004] In certain embodiments, the invention provides a compound having a structure selected from Formula I, Formula II, Formula III, Formula IV, Formula V, and Formula VI:



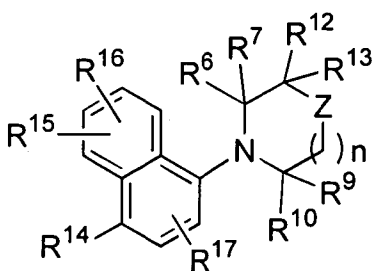
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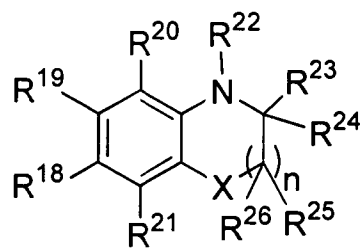
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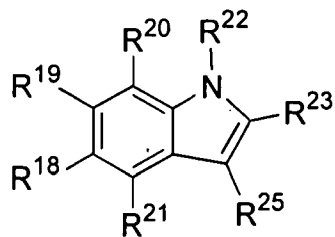
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(IV)



(V)



(VI)

wherein:

[005]  $R^1$  and  $R^2$  are each independently selected from hydrogen, F, Cl, Br, I,  $OR^A$ ,  $SR^A$ ,  $NO_2$ , CN, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, an optionally substituted  $C_1$ - $C_4$  heteroalkyl,  $COR^A$ ,  $CO_2R^A$ ,  $CONR^AR^B$ ,  $SOR^A$ ,  $SO_2R^A$ , and  $SO_2NR^AR^B$ ,  $NHCOR^A$ , and  $NHCONR^AR^B$ , provided that at least one of  $R^1$  and  $R^2$  is not hydrogen;

[006]  $R^3$ ,  $R^{3a}$ ,  $R^4$ , and  $R^5$  are each independently selected from hydrogen, F, Cl,  $OR^A$ , an optionally substituted  $C_1$ - $C_4$  alkyl, and an optionally substituted  $C_1$ - $C_4$  haloalkyl;

[007] wherein if  $R^1$  is  $NO_2$  and  $R^{3a}$  is F, then at least one of  $R^2$  and  $R^4$  and  $R^5$  is not hydrogen; and wherein if  $R^1$  is  $NO_2$  and  $R^3$  is F, then Z is not O;

[008]  $R^6$ ,  $R^7$ ,  $R^{10}$ , and  $R^{11}$  are each independently selected from hydrogen, an optionally substituted  $C_1$ - $C_6$  alkyl, an optionally substituted  $C_1$ - $C_6$  haloalkyl, an optionally substituted  $C_1$ - $C_6$  heteroalkyl, an optionally substituted  $C_2$ - $C_6$  alkynyl, and an optionally substituted  $C_2$ - $C_6$  alkenyl;

[009]  $R^{6a}$  and  $R^{7a}$  are each independently selected from hydrogen, an optionally substituted  $C_1$ - $C_6$  alkyl, an optionally substituted  $C_1$ - $C_6$  haloalkyl, an optionally substituted  $C_1$ - $C_6$  heteroalkyl, an optionally substituted  $C_2$ - $C_6$  alkynyl, and an optionally substituted  $C_2$ - $C_6$  alkenyl; or  $R^{6a}$  and  $R^{7a}$  together form a carbonyl;

[010]  $R^8$  and  $R^9$  are each independently selected from hydrogen, an optionally substituted  $C_1$ - $C_8$  alkyl, an optionally substituted  $C_2$ - $C_8$  alkenyl, an optionally

substituted C<sub>1</sub>-C<sub>8</sub> haloalkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> haloalkenyl, C<sub>1</sub>-C<sub>8</sub> heteroalkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> heteroalkenyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> alkynyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> haloalkynyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, CH(R<sup>D</sup>)OR<sup>A</sup>, CH(R<sup>D</sup>)NR<sup>A</sup>R<sup>B</sup>, and (CH<sub>2</sub>)<sub>m</sub>R<sup>C</sup>;

[011] R<sup>12</sup> and R<sup>13</sup> are each independently selected from hydrogen, F, Cl, OR<sup>A</sup>, NR<sup>A</sup>R<sup>B</sup>, SR<sup>A</sup>, an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>6</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>6</sub> heteroalkyl, an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, and (CH<sub>2</sub>)<sub>m</sub>R<sup>C</sup>;

[012] R<sup>14</sup> and R<sup>15</sup> are each independently selected from hydrogen, F, Cl, Br, I, OR<sup>A</sup>, SR<sup>A</sup>, NO<sub>2</sub>, CN, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> heteroalkyl, NHCOR<sup>A</sup>, NHCONR<sup>A</sup>R<sup>B</sup>, COR<sup>A</sup>, CO<sub>2</sub>R<sup>A</sup>, CONR<sup>A</sup>R<sup>B</sup>, SOR<sup>A</sup>, SO<sub>2</sub>R<sup>A</sup>, and SO<sub>2</sub>NR<sup>A</sup>R<sup>B</sup>;

[013] R<sup>16</sup> and R<sup>17</sup> are each independently selected from hydrogen, F, Cl, OR<sup>A</sup>, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, and an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl;

[014] R<sup>18</sup> and R<sup>19</sup> are each independently selected from hydrogen, F, Cl, Br, I, OR<sup>A</sup>, SR<sup>A</sup>, NO<sub>2</sub>, CN, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> heteroalkyl, NHCOR<sup>A</sup>, NHCONR<sup>A</sup>R<sup>B</sup>, COR<sup>A</sup>, CO<sub>2</sub>R<sup>A</sup>, CONR<sup>A</sup>R<sup>B</sup>, SOR<sup>A</sup>, SO<sub>2</sub>R<sup>A</sup>, and SO<sub>2</sub>NR<sup>A</sup>R<sup>B</sup>;

[015] R<sup>20</sup> and R<sup>21</sup> are each independently selected from hydrogen, F, Cl, OR<sup>A</sup>, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, and an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl;

[016] wherein if  $R^{18}$  is  $\text{NO}_2$  and X is O, then at least one of  $R^{19}$ ,  $R^{20}$ , and  $R^{21}$  is not hydrogen, and wherein if  $R^{19}$  is  $\text{NO}_2$  and X is C, then at least one of  $R^{18}$ ,  $R^{20}$ , and  $R^{21}$  is not hydrogen;

[017]  $R^{22}$  is selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_4$  alkyl, an optionally substituted  $\text{C}_1\text{-C}_4$  haloalkyl, an optionally substituted  $\text{C}_1\text{-C}_4$  heteroalkyl,  $\text{COR}^6$ ,  $\text{CO}_2\text{R}^A$ ,  $\text{CONR}^A\text{R}^B$ ,  $\text{SO}_2\text{R}^A$ , an optionally substituted aryl, an optionally substituted heteroaryl,  $\text{CH}_2\text{CH}(\text{R}^D)\text{OR}^A$ ,  $\text{CH}_2\text{CH}(\text{R}^D)\text{NR}^A\text{R}^B$ , and  $(\text{CH}_2)_m\text{R}^C$ , wherein the optionally substituted aryl or optionally substituted heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, CN,  $\text{OR}^A$ ,  $\text{NO}_2$ ,  $\text{NR}^A\text{R}^B$ ,  $\text{SR}^A$ ,  $\text{SOR}^A$ ,  $\text{SO}_2\text{R}^A$ , an optionally substituted  $\text{C}_1\text{-C}_4$  alkyl, an optionally substituted  $\text{C}_1\text{-C}_4$  haloalkyl, and an optionally substituted  $\text{C}_1\text{-C}_4$  heteroalkyl;

[018]  $R^{23}$  and  $R^{24}$  are each independently selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_8$  alkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkenyl, an optionally substituted  $\text{C}_1\text{-C}_8$  haloalkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  haloalkenyl, an optionally substituted  $\text{C}_1\text{-C}_8$  heteroalkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  heteroalkenyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkynyl, an optionally substituted  $\text{C}_2\text{-C}_8$  haloalkynyl, an optionally substituted  $\text{C}_2\text{-C}_8$  heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl,  $\text{CH}(\text{R}^D)\text{OR}^A$ ,  $\text{CH}(\text{R}^D)\text{NR}^A\text{R}^B$ , and  $(\text{CH}_2)_m\text{R}^C$ ; or  $R^{23}$  and  $R^{24}$  together form a carbonyl group, provided that if  $R^{18}$  is  $\text{NO}_2$  and X is NH, then  $R^{23}$  and  $R^{24}$  do not together form a carbonyl group; or

[019]  $R^{22}$  and  $R^{23}$  are optionally linked to form a ring; or

[020]  $R^{23}$  and  $R^{25}$  are optionally linked to form a ring;

[021] X is selected from O, S,  $CR^A R^B$ ,  $NR^D$ , and a bond;

[022] wherein if X is  $CR^A R^B$  or a bond, then  $R^{25}$  and  $R^{26}$  are each independently selected from a halogen,  $OR^A$ ,  $NR^A R^B$ , hydrogen, an optionally substituted  $C_1$ - $C_8$  alkyl, an optionally substituted  $C_2$ - $C_8$  alkenyl, an optionally substituted  $C_1$ - $C_8$  haloalkyl, an optionally substituted  $C_2$ - $C_8$  haloalkenyl, an optionally substituted  $C_1$ - $C_8$  heteroalkyl, an optionally substituted  $C_2$ - $C_8$  heteroalkenyl, an optionally substituted  $C_2$ - $C_8$  alkynyl, an optionally substituted  $C_2$ - $C_8$  haloalkynyl, an optionally substituted  $C_2$ - $C_8$  heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, and  $(CH_2)_m R^C$ ; or  $R^{25}$  and  $R^{26}$  together form a carbonyl group;

[023] and wherein if X is O, S, or  $NR^D$ , then  $R^{25}$  and  $R^{26}$  are each independently selected from hydrogen, an optionally substituted  $C_1$ - $C_8$  alkyl, an optionally substituted  $C_2$ - $C_8$  alkenyl, an optionally substituted  $C_1$ - $C_8$  haloalkyl, an optionally substituted  $C_2$ - $C_8$  haloalkenyl, an optionally substituted  $C_1$ - $C_8$  heteroalkyl, an optionally substituted  $C_2$ - $C_8$  heteroalkenyl, an optionally substituted  $C_2$ - $C_8$  alkynyl, an optionally substituted  $C_2$ - $C_8$  haloalkynyl, an optionally substituted  $C_2$ - $C_8$  heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, and  $(CH_2)_m R^C$ ; or  $R^{25}$  and  $R^{26}$  together form a carbonyl group;

[024]  $R^A$  and  $R^B$  are each independently selected from hydrogen, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, and an optionally substituted  $C_1$ - $C_4$  heteroalkyl;

[025]  $R^C$  is selected from an optionally substituted aryl and an optionally substituted heteroaryl that is optionally with a substituent selected from F, Cl, Br, I, CN,  $OR^A$ ,  $NO_2$ ,  $NR^A R^B$ ,  $SR^A$ ,  $SOR^A$ ,  $SO_2 R^A$ , an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, and an optionally substituted  $C_1$ - $C_4$  heteroalkyl;

[026]  $R^D$  is selected from hydrogen, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, and an optionally substituted  $C_1$ - $C_4$  heteroalkyl;

[027] Z is selected from O, S,  $CR^A R^B$ , and  $NR^D$ ;

[028] n is 0, 1, or 2; and

[029] m is 1 or 2.

[030] In certain embodiments, the invention provides a compound selected from: (a) N,N'-bis(2,2,2-trifluoroethyl)-3-methyl-4-nitroaniline; N,N'-bis(2,2,2-trifluoroethyl)-4-nitroaniline; 5-(2,2,2-trifluoroethyl)amino-2-bromobenzotrifluoride; 4-N,N'-bis(2,2,2-trifluoroethyl)amino-2-trifluoromethylbenzonitrile; (R)-N-4-nitrophenyl-5-(dimethyl-tert-butylsilyloxymethyl)-2-pyrrolidone; (R)-N-4-nitrophenyl-5-hydroxymethyl-2-pyrrolidone; (R)-N-(4-nitro-3-trifluoromethylphenyl)-2-dimethyl-tert-butylsilyloxymethylpyrrolidine; (R)-N-(4-nitro-3-trifluoromethylphenyl)-2-hydroxymethylpyrrolidine; (R)-N-(4-nitrophenyl)-2-hydroxymethylpyrrolidine; (R)-N-(3-Trifluoromethyl-4-nitrophenyl)-2-formylpyrrolidine; N-(3-Trifluoromethyl-4-nitrophenyl)-2-(R)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; N-(3-Trifluoromethyl-4-nitrophenyl)-2-(R)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; (S)-N-(4-nitrophenyl)-2-hydroxymethylpyrrolidine; N-(4-nitrophenyl)-2-(R)-(1-(S)-

hydroxy-2,2,2-trifluoroethyl)pyrrolidine; N-(4-nitrophenyl)-2-(R)-(1-(R)-hydroxy-2,2,2-trifluoroethyl); N-(4-nitrophenyl)-2-(S)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; and N-(4-nitrophenyl)-2-(S)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; and (b) a pharmaceutically acceptable salt, ester, amide, or prodrug thereof.

[031] In certain embodiments, the invention provides methods for modulating an activity of an androgen receptor comprising contacting a androgen receptor with at least one compound of the present invention. In certain such embodiments, the androgen receptor is in a cell.

[032] In certain embodiments, the invention provides methods for identifying a compound that is capable of modulating an activity of a androgen receptor, comprising contacting a cell expressing a androgen receptor with a compound of the present invention; and monitoring an effect of the compound upon the cell.

[033] In certain embodiments, the invention provides methods for treating a patient comprising administering to the patient a compound of the present invention. In certain of such embodiments, the patient has a condition selected from acne, male-pattern baldness, wasting diseases, hirsutism, hypogonadism, osteoporoses, infertility, impotence, and cancer.

[034] In certain embodiments, the invention provides methods for stimulating hematopoiesis. In certain embodiments, the invention provides methods for contraception. In certain embodiments, the invention provides methods for improving

athletic performance.

[035] In certain embodiments, the invention provides a selective androgen receptor modulator. In certain embodiments, the invention provides a selective androgen receptor agonist. In certain embodiments, the invention provides a selective androgen receptor antagonist. In certain embodiments, the invention provides an androgen receptor partial agonist. In certain embodiments, the invention provides a selective androgen receptor binding compound.

[036] In certain embodiments, the invention provides methods for modulating at least one activity of a androgen receptor. Certain of such methods comprise contacting an androgen receptor with one or more compounds of the present invention.

[037] In certain embodiments, the invention provides methods for treating a patient comprising administering to the patient a compound of the present invention.

[038] In certain embodiments, the invention provides methods for treating a condition including, but not limited to, acne, male-pattern baldness, wasting diseases, hirsutism, hypogonadism, osteoporoses, infertility, impotence, and cancer.

[039] In certain embodiments, the invention provides a pharmaceutical agent comprising: i) a physiologically acceptable carrier, diluent, and/or excipient; and ii) one or more compounds of the present invention.

#### Detailed Description

[040] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not

restrictive of the invention claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. In this application, the use of “or” means “and/or” unless stated otherwise. Furthermore, use of the term “including” as well as other forms, such as “includes,” and “included,” is not limiting.

[041] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

#### Definitions

[042] Unless specific definitions are provided, the nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (*e.g.*, electroporation, lipofection). Reactions and purification techniques may be performed *e.g.*, using kits according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures may be generally

performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. *See e.g.*, Sambrook et al. *Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference for any purpose.

[043] As used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

[044] The term “selective binding compound” refers to a compound that selectively binds to any portion of one or more target receptors.

[045] The term “selective androgen receptor binding compound” refers to a compound that selectively binds to any portion of an androgen receptor.

[046] The term “selectively binds” refers to the ability of a selective binding compound to bind to a target receptor with greater affinity than it binds to a non-target receptor. In certain embodiments, specific binding refers to binding to a target with an affinity that is at least 10, 50, 100, 250, 500, or 1000 times greater than the affinity for a non-target.

[047] The term “target receptor” refers to a molecule or a portion of a receptor capable of being bound by a selective binding compound. In certain embodiments, a target receptor is an androgen receptor.

[048] The term “modulator” refers to a compound that alters an activity of a molecule. For example, a modulator may cause an increase or decrease in the

magnitude of a certain activity of a molecule compared to the magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a molecule. In certain embodiments, an inhibitor completely prevents one or more activities of a molecule. In certain embodiments, a modulator is an activator, which increases the magnitude of at least one activity of a molecule. In certain embodiments the presence of a modulator results in an activity that does not occur in the absence of the modulator.

[049] The term “selective modulator” refers to a compound that selectively modulates a target activity.

[050] The term “selective androgen receptor modulator” refers to a compound that selectively modulates at least one activity associated with a androgen receptor.

[051] The term “selectively modulates” refers to the ability of a selective modulator to modulate a target activity to a greater extent than it modulates a non-target activity.

[052] The term “target activity” refers to a biological activity capable of being modulated by a selective modulator. Certain exemplary target activities include, but are not limited to, binding affinity, signal transduction, enzymatic activity, and tumor growth.

[053] The term “receptor mediated activity” refers any biological activity that results, either directly or indirectly, from binding of a ligand to a receptor.

[054] The term “agonist” refers to a compound, the presence of which results

in a biological activity of a receptor that is the same as the biological activity resulting from the presence of a naturally occurring ligand for the receptor.

[055] The term "partial agonist" refers to a compound the presence of which results in a biological activity of a receptor that is of the same type as that resulting from the presence of a naturally occurring ligand for the receptor, but of a lower magnitude.

[056] The term "antagonist" refers to a compound, the presence of which results in a decrease in the magnitude of a biological activity of a receptor. In certain embodiments, the presence of an antagonist results in complete inhibition of a biological activity of a receptor.

[057] The term "alkyl" refers to a hydrocarbon group. An alkyl group may be a "saturated alkyl," which means that it does not contain any alkene or alkyne groups. An alkyl group may be an "unsaturated alkyl," which means that it comprises at least one alkene or alkyne group. An alkyl, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

[058] In certain embodiments, an alkyl comprises 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that an alkyl group may comprise only 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the term "alkyl" also includes instances where no numerical range of carbon atoms is designated).

[059] The term “lower alkyl” refers to an alkyl comprising 1 to 5 carbon atoms. The term “medium alkyl” refers to an alkyl comprising 5 to 10 carbon atoms. An alkyl may be designated as “C<sub>1</sub>-C<sub>4</sub> alkyl” or similar designations. By way of example only, “C<sub>1</sub>-C<sub>4</sub> alkyl” indicates an alkyl having one, two, three, or four carbon atoms, i.e., the alkyl is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Alkyls may be substituted or unsubstituted. Alkyls include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like, each of which may be optionally substituted.

[060] The term “alkenyl” refers to an alkyl group comprising at least one carbon-carbon double bond.

[061] The term “alkynyl” refers to an alkyl group comprising at least one carbon-carbon triple bond.

[062] The term “haloalkyl” refers to an alkyl in which at least one hydrogen atom is replaced with a halogen atom. In certain of the embodiments in which two or more hydrogen atom are replaced with halogen atoms, the halogen atoms are all the same as one another. In certain of such embodiments, the halogen atoms are not all the same as one another.

[063] The term “heteroalkyl” refers to a group comprising an alkyl and one or more heteroatoms. Certain heteroalkyls are acylalkyls, in which the one or more heteroatoms are within an alkyl chain. Examples of heteroalkyls include, but are not

limited to,  $\text{CH}_3\text{C}(=\text{O})\text{CH}_2-$ ,  $\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{CH}_2-$ ,  $\text{CH}_3\text{CH}_2\text{C}(=\text{O})\text{CH}_2\text{CH}_2-$ ,  $\text{CH}_3\text{C}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $\text{CH}_3\text{OCH}_2\text{CH}_2-$ ,  $\text{CH}_3\text{NHCH}_2-$ , and the like.

[064] The term “heterohaloalkyl” refers to a heteroalkyl in which at least one hydrogen atom is replaced with a halogen atom.

[065] The term “carbocycle” refers to a group comprising a covalently closed ring, wherein each of the atoms forming the ring is a carbon atom. Carbocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycles may be optionally substituted.

[066] The term “heterocycle” refers to a group comprising a covalently closed ring wherein at least one atom forming the ring is a heteroatom. Heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Heterocycles may be optionally substituted. Binding to a heterocycle can be at a heteroatom or via a carbon atom. For example, binding for benzo-fused derivatives, may be via a carbon of the benzenoid ring.

[067] The term “heteroatom” refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from oxygen, sulfur, nitrogen, and phosphorus, but are not limited to those atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms may all be the same as one another, or some or all of the two or more heteroatoms may each be different from the others.

[068] The term “aromatic” refers to a group comprising a covalently closed

ring having a delocalized  $\pi$ -electron system. Aromatic rings may be formed by five, six, seven, eight, nine, or more than nine atoms. Aromatics may be optionally substituted. Examples of aromatic groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl. The term aromatic includes, for example, benzenoid groups, connected via one of the ring-forming carbon atoms, and optionally carrying one or more substituents selected from an aryl, a heteroaryl, a cycloalkyl, a non-aromatic heterocycle, a halo, a hydroxy, an amino, a cyano, a nitro, an alkylamido, an acyl, a C<sub>1-6</sub> alkoxy, a C<sub>1-6</sub> alkyl, a C<sub>1-6</sub> hydroxyalkyl, a C<sub>1-6</sub> aminoalkyl, a C<sub>1-6</sub> alkylamino, an alkylsulfenyl, an alkylsulfinyl, an alkylsulfonyl, an sulfamoyl, or a trifluoromethyl. In certain embodiments, an aromatic group is substituted at one or more of the para, meta, and/or ortho positions. Examples of aromatic groups comprising substitutions include, but are not limited to, phenyl, 3-halophenyl, 4-halophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, dimethylphenyl, naphthyl, hydroxynaphthyl, hydroxymethylphenyl, (trifluoromethyl)phenyl, alkoxyphenyl, 4-morpholin-4-ylphenyl, 4-pyrrolidin-1-ylphenyl, 4-pyrazolylphenyl, 4-triazolylphenyl, and 4-(2-oxopyrrolidin-1-yl)phenyl.

[069] The term “aryl” refers to an aromatic group wherein each of the atoms forming the ring is a carbon atom. Aryl rings may be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups may be optionally substituted.

[070] The term “heteroaryl” refers to an aromatic group wherein at least one atom forming the aromatic ring is a heteroatom. Heteroaryl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Heteroaryl groups may be optionally substituted. Examples of heteroaryl groups include, but are not limited to, aromatic C<sub>3-8</sub> heterocyclic groups comprising one oxygen or sulfur atom or up to four nitrogen atoms, or a combination of one oxygen or sulfur atom and up to two nitrogen atoms, and their substituted as well as benzo- and pyrido-fused derivatives, for example, connected via one of the ring-forming carbon atoms. In certain embodiments, heteroaryl groups are optionally substituted with one or more substituents, independently selected from halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-hydroxyalkyl, C<sub>1-6</sub>-aminoalkyl, C<sub>1-6</sub>-alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, or trifluoromethyl. Examples of heteroaryl groups include, but are not limited to, unsubstituted and mono- or di-substituted derivatives of furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, indole, oxazole, benzoxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, isothiazole, imidazole, benzimidazole, pyrazole, indazole, tetrazole, quinoline, isoquinoline, pyridazine, pyrimidine, purine and pyrazine, furazan, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, triazole, benzotriazole, pteridine, phenoxazole, oxadiazole, benzopyrazole, quinolizine, cinnoline, phthalazine, quinazoline, and quinoxaline. In some embodiments, the substituents are halo, hydroxy, cyano, O-C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkyl, hydroxy-C<sub>1-6</sub>-alkyl, and amino-C<sub>1-6</sub>-alkyl.

[071] The term “non-aromatic ring” refers to a group comprising a covalently closed ring that does not have a delocalized  $\pi$ -electron system.

[072] The term “cycloalkyl” refers to a group comprising a non-aromatic ring wherein each of the atoms forming the ring is a carbon atom. Cycloalkyl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Cycloalkyls may be optionally substituted. In certain embodiments, a cycloalkyl comprises one or more unsaturated bonds. Examples of cycloalkyls include, but are not limited to, cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclopentadiene, cyclohexane, cyclohexene, 1,3-cyclohexadiene, 1,4-cyclohexadiene, cycloheptane, and cycloheptene.

[073] The term “non-aromatic heterocycle” refers to a group comprising a non-aromatic ring wherein one or more atoms forming the ring is a heteroatom. Non-aromatic heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Non-aromatic heterocycles may be optionally substituted. In certain embodiments, non-aromatic heterocycles comprise one or more carbonyl or thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples of non-aromatic heterocycles include, but are not limited to, lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, tetrahydrothiopyran, 4*H*-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2*H*-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine,

hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane.

[074] The term “arylalkyl” refers to a group comprising an aryl group bound to an alkyl group.

[075] The term “carbocycloalkyl” refers to a group comprising a carbocyclic cycloalkyl ring. Carbocycloalkyl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycloalkyl groups may be optionally substituted.

[076] The term “ring” refers to any covalently closed structure. Rings include, for example, carbocycles (*e.g.*, aryls and cycloalkyls), heterocycles (*e.g.*, heteroaryl and non-aromatic heterocycles), aromatics (*e.g.*, aryls and heteroaryl), and non-aromatics (*e.g.*, cycloalkyls and non-aromatic heterocycles). Rings may be optionally substituted. Rings may form part of a ring system.

[077] The term “ring system” refers to two or more rings, wherein two or more of the rings are fused. The term “fused” refers to structures in which two or more rings share one or more bonds.

[078] The substituent “R” appearing by itself and without a number designation refers to a substituent selected from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a

ring carbon) and non-aromatic heterocycle (bonded through a ring carbon).

[079] The term "O-carboxy" refers to a group of formula  $\text{RC}(=\text{O})\text{O}-$ .

[080] The term "C-carboxy" refers to a group of formula  $-\text{C}(=\text{O})\text{OR}$ .

[081] The term "acetyl" refers to a group of formula  $-\text{C}(=\text{O})\text{CH}_3$ .

[082] The term "trihalomethanesulfonyl" refers to a group of formula  $\text{X}_3\text{CS}(=\text{O})_2-$  where X is a halogen.

[083] The term "cyano" refers to a group of formula  $-\text{CN}$ .

[084] The term "isocyanato" refers to a group of formula  $-\text{NCO}$ .

[085] The term "thiocyanato" refers to a group of formula  $-\text{CNS}$ .

[086] The term "isothiocyanato" refers to a group of formula  $-\text{NCS}$ .

[087] The term "sulfinyl" refers to a group of formula  $-\text{S}(=\text{O})-\text{R}$ .

[088] The term "S-sulfonamido" refers to a group of formula  $-\text{S}(=\text{O})_2\text{NR}$ .

[089] The term "N-sulfonamido" refers to a group of formula  $\text{RS}(=\text{O})_2\text{NH}-$ .

[090] The term "trihalomethanesulfonamido" refers to a group of formula  $\text{X}_3\text{CS}(=\text{O})_2\text{NR}-$ .

[091] The term "O-carbamyl" refers to a group of formula  $-\text{OC}(=\text{O})-\text{NR}$ .

[092] The term "N-carbamyl" refers to a group of formula  $\text{ROC}(=\text{O})\text{NH}-$ .

[093] The term "O-thiocarbamyl" refers to a group of formula  $-\text{OC}(=\text{S})-\text{NR}$ .

[094] The term "N-thiocarbamyl" refers to a group of formula  $\text{ROC}(=\text{S})\text{NH}-$ .

[095] The term "C-amido" refers to a group of formula  $-\text{C}(=\text{O})-\text{NR}_2$ .

[096] The term "N-amido" refers to a group of formula  $\text{RC}(=\text{O})\text{NH}-$ .

[097] The term “ester” refers to a chemical moiety with formula  $-(R)_n-COOR'$ , where R and R' are independently selected from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon), where n is 0 or 1.

[098] The term “amide” refers to a chemical moiety with formula  $-(R)_n-C(O)NHR'$  or  $-(R)_n-NHC(O)R'$ , where R and R' are independently selected from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), where n is 0 or 1. In certain embodiments, an amide may be an amino acid or a peptide.

[099] The terms “amine,” “hydroxy,” and “carboxyl” include such groups that have been esterified or amidified. Procedures and specific groups used to achieve esterification and amidification are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3<sup>rd</sup> Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein in its entirety.

[0100] Unless otherwise indicated, the term “optionally substituted,” refers to a group in which none, one, or more than one of the hydrogen atoms has been replaced with one or more group(s) individually and independently selected from: cycloalkyl, aryl, heteroaryl, non-aromatic heterocycle, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido,

C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives of amino groups. Such protective derivatives (and protecting groups that may form such protective derivatives) are known to those of skill in the art and may be found in references such as Greene and Wuts, above. In embodiments in which two or more hydrogen atoms have been substituted, the substituent groups may together form a ring.

[0101] The term “carrier” refers to a compound that facilitates the incorporation of another compound into cells or tissues. For example, dimethyl sulfoxide (DMSO) is a commonly used carrier for improving incorporation of certain organic compounds into cells or tissues.

[0102] The term "pharmaceutical agent" refers to a chemical compound or composition capable of inducing a desired therapeutic effect in a patient. In certain embodiments, a pharmaceutical agent comprises an active agent, which is the agent that induces the desired therapeutic effect. In certain embodiments, a pharmaceutical agent comprises a prodrug. In certain embodiments, a pharmaceutical agent comprises inactive ingredients such as carriers, excipients, and the like.

[0103] The term “therapeutically effective amount” refers to an amount of a pharmaceutical agent sufficient to achieve a desired therapeutic effect.

[0104] The term “prodrug” refers to an pharmaceutical agent that is converted from a less active form into a corresponding more active form *in vivo*.

[0105] The term “pharmaceutically acceptable” refers to a formulation of a compound that does not significantly abrogate the biological activity, a pharmacological activity and/or other properties of the compound when the formulated compound is administered to a patient. In certain embodiments, a pharmaceutically acceptable formulation does not cause significant irritation to a patient.

[0106] The term “co-administer” refers to administering more than one pharmaceutical agent to a patient. In certain embodiments, co-administered pharmaceutical agents are administered together in a single dosage unit. In certain embodiments, co-administered pharmaceutical agents are administered separately. In certain embodiments, co-administered pharmaceutical agents are administered at the same time. In certain embodiments, co-administered pharmaceutical agents are administered at different times.

[0107] The term “patient” includes human and animal subjects.

[0108] The term "substantially pure" means an object species (*e.g.*, compound) is the predominant species present (*i.e.*, on a molar basis it is more abundant than any other individual species in the composition). In certain embodiments, a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all species present. In certain embodiments, a substantially pure composition will comprise more than about 80%, 85%, 90%, 95%, or 99% of all species present in the composition. In certain embodiments, the object species is purified to essential homogeneity (contaminant species cannot be detected in

the composition by conventional detection methods) wherein the composition consists essentially of a single species.

[0109] The term “tissue-selective” refers to the ability of a compound to modulate a biological activity in one tissue to a greater or lesser degree than it modulates a biological activity in another tissue. The biological activities in the different tissues may be the same or they may be different. The biological activities in the different tissues may be mediated by the same type of target receptor. For example, in certain embodiments, a tissue-selective compound may modulate a androgen receptor mediated biological activity in one tissue and fail to modulate, or modulate to a lesser degree, a androgen receptor mediated biological activity in another tissue type.

[0110] The term “monitoring” refers to observing an effect or absence of any effect. In certain embodiments, one monitors cells after contacting those cells with a compound of the present invention. Examples of effects that may be monitored include, but are not limited to, changes in cell phenotype, cell proliferation, androgen receptor activity, or the interaction between a androgen receptor and a natural binding partner.

[0111] The term “cell phenotype” refers to physical or biological characteristics. Examples of characteristics that constitute phenotype included, but are not limited to, cell size, cell proliferation, cell differentiation, cell survival, apoptosis (cell death), or the utilization of a metabolic nutrient (*e.g.*, glucose uptake). Certain changes or the absence of changes in cell phenotype are readily monitored using techniques known in the art.

[0112] The term “cell proliferation” refers to the rate at which cells divide. The number of cells growing in a vessel can be quantified by a person skilled in the art (*e.g.*, by counting cells in a defined area using a light microscope, or by using laboratory apparatus that measure the density of cells in an appropriate medium). One skilled in that art can calculate cell proliferation by determining the number of cells at two or more times.

[0113] The term “contacting” refers to bringing two or more materials into close enough proximity that they may interact. In certain embodiments, contacting can be accomplished in a vessel such as a test tube, a petri dish, or the like. In certain embodiments, contacting may be performed in the presence of additional materials. In certain embodiments, contacting may be performed in the presence of cells. In certain of such embodiments, one or more of the materials that are being contacted may be inside a cell. Cells may be alive or may be dead. Cells may or may not be intact.

Certain compounds

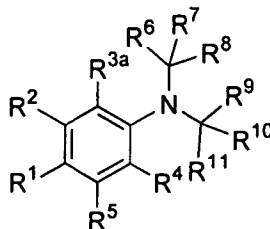
[0114] Certain compounds that bind to androgen receptors and/or modulate an activity of such receptors play a role in health (*e.g.*, normal growth, development, and/or absence of disease). In certain embodiments, selective androgen receptor modulators and/or binding compounds are useful for treating any of a variety of diseases or conditions.

[0115] Certain compounds have been previously described as receptor modulators or as possible receptor modulators. *See e.g.*, U. S. Patent Nos. 6,462,038,

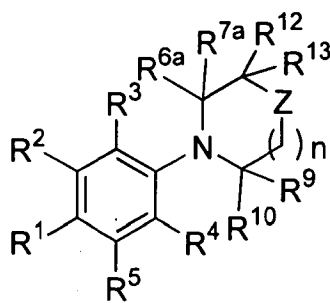
5,693,646; 6,380,207; 6,506,766; 5,688,810; 5,696,133; 6,569,896, 6,673,799;  
4,636,505; 4,097,578; 3,847,988; U.S. Application No. 10/209,461 (Pub. No. US  
2003/0055094); WO 01/27086; WO 02/22585; Zhi, *et.al. Bioorganic & Medicinal  
Chemistry Letters* 2000, 10, 415-418; Pooley, *et. al., J. Med. Chem.* 1998, 41, 3461;  
Hamann, *et al. J. Med. Chem.* 1998, 41(4), 623; and Yin, *et al., Molecular  
Pharmacology*, 2003, 63 (1), 211-223 the entire disclosures of which are incorporated  
in their entirety.

[0116] In certain embodiments, the present invention provides selective  
androgen receptor modulators. In certain embodiments, the invention provides selective  
androgen receptor binding agents. In certain embodiments, the invention provides  
methods of making and methods of using selective androgen receptor modulators and/or  
selective androgen binding agents. In certain embodiments, selective androgen  
modulators are agonists, partial agonists, and/or antagonists for the androgen receptor.

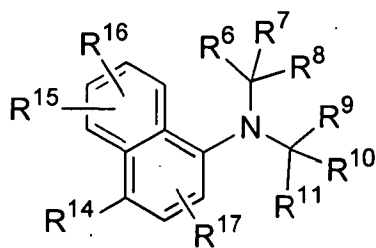
[0117] In certain embodiments, the present invention relates to a compound of a  
compound having a structure selected from Formula I, Formula II, Formula III, Formula  
IV, Formula V, and Formula VI:



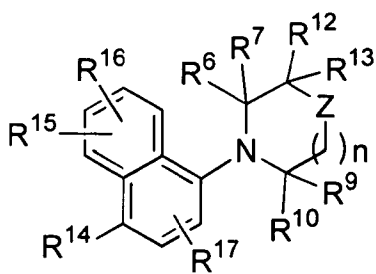
(I)



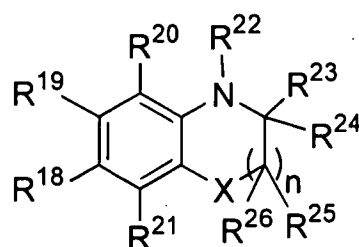
(II)



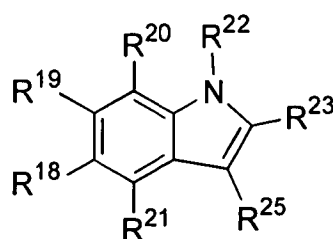
(III)



(IV)



(V)



(VI)

[0118] In certain embodiments,  $R^1$  and  $R^2$  are each independently selected from hydrogen, F, Cl, Br, I,  $OR^A$ ,  $SR^A$ ,  $NO_2$ , CN, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, an optionally substituted  $C_1$ - $C_4$  heteroalkyl,  $COR^A$ ,  $CO_2R^A$ ,  $CONR^AR^B$ ,  $SOR^A$ ,  $SO_2R^A$ , and  $SO_2NR^AR^B$ ,  $NHCOR^A$ ,  $NHCONR^AR^B$ . In certain embodiments,  $R^1$  and  $R^2$  are not both hydrogen.

[0119] In certain embodiments,  $R^3$ ,  $R^{3a}$ ,  $R^4$ , and  $R^5$  are each independently selected from hydrogen, F, Cl,  $OR^A$ , an optionally substituted  $C_1$ - $C_4$  alkyl, and an optionally substituted  $C_1$ - $C_4$  haloalkyl. In certain embodiments, if  $R^1$  is  $NO_2$  and  $R^{3a}$  is F, then at least one of  $R^2$  and  $R^4$  and  $R^5$  is not hydrogen. In certain embodiments, if  $R^1$  is  $NO_2$  and  $R^3$  is F, then Z is not O.

[0120] In certain embodiments,  $R^6$ ,  $R^7$ ,  $R^{10}$ , and  $R^{11}$  are each independently selected from hydrogen, an optionally substituted  $C_1$ - $C_6$  alkyl, an optionally substituted

C<sub>1</sub>-C<sub>6</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>6</sub> heteroalkyl, an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, and an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl.

[0121] In certain embodiments, R<sup>6a</sup> and R<sup>7a</sup> are each independently selected from hydrogen, an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>6</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>6</sub> heteroalkyl, an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, and an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl. In certain embodiments, R<sup>6a</sup> and R<sup>7a</sup> together form a carbonyl.

[0122] In certain embodiments, R<sup>8</sup> and R<sup>9</sup> are each independently selected from hydrogen, an optionally substituted C<sub>1</sub>-C<sub>8</sub> alkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> alkenyl, an optionally substituted C<sub>1</sub>-C<sub>8</sub> haloalkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> haloalkenyl, C<sub>1</sub>-C<sub>8</sub> heteroalkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> heteroalkenyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> alkynyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> haloalkynyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, CH(R<sup>D</sup>)OR<sup>A</sup>, CH(R<sup>D</sup>)NR<sup>A</sup>R<sup>B</sup>, and (CH<sub>2</sub>)<sub>m</sub>R<sup>C</sup>.

[0123] In certain embodiments, R<sup>12</sup> and R<sup>13</sup> are each independently selected from hydrogen, F, Cl, OR<sup>A</sup>, NR<sup>A</sup>R<sup>B</sup>, SR<sup>A</sup>, an optionally substituted C<sub>1</sub>-C<sub>6</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>6</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>6</sub> heteroalkyl, an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkynyl, an optionally substituted C<sub>2</sub>-C<sub>6</sub> alkenyl, and (CH<sub>2</sub>)<sub>m</sub>R<sup>C</sup>.

[0124] In certain embodiments, R<sup>14</sup> and R<sup>15</sup> are each independently selected from hydrogen, F, Cl, Br, I, OR<sup>A</sup>, SR<sup>A</sup>, NO<sub>2</sub>, CN, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl,

an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> heteroalkyl, NHCOR<sup>A</sup>, NHCONR<sup>A</sup>R<sup>B</sup>, COR<sup>A</sup>, CO<sub>2</sub>R<sup>A</sup>, CONR<sup>A</sup>R<sup>B</sup>, SOR<sup>A</sup>, SO<sub>2</sub>R<sup>A</sup>, and SO<sub>2</sub>NR<sup>A</sup>R<sup>B</sup>.

[0125] In certain embodiments, R<sup>16</sup> and R<sup>17</sup> are each independently selected from hydrogen, F, Cl, OR<sup>A</sup>, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, and an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl.

[0126] In certain embodiments, R<sup>18</sup> and R<sup>19</sup> are each independently selected from hydrogen, F, Cl, Br, I, OR<sup>A</sup>, SR<sup>A</sup>, NO<sub>2</sub>, CN, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> heteroalkyl, NHCOR<sup>A</sup>, NHCONR<sup>A</sup>R<sup>B</sup>, COR<sup>A</sup>, CO<sub>2</sub>R<sup>A</sup>, CONR<sup>A</sup>R<sup>B</sup>, SOR<sup>A</sup>, SO<sub>2</sub>R<sup>A</sup>, and SO<sub>2</sub>NR<sup>A</sup>R<sup>B</sup>.

[0127] In certain embodiments, R<sup>20</sup> and R<sup>21</sup> are each independently selected from hydrogen, F, Cl, OR<sup>A</sup>, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, and an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl.

[0128] In certain embodiments, R<sup>22</sup> is selected from hydrogen, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> heteroalkyl, COR<sup>A</sup>, CO<sub>2</sub>R<sup>A</sup>, CONR<sup>A</sup>R<sup>B</sup>, SO<sub>2</sub>R<sup>A</sup>, an optionally substituted aryl, an optionally substituted heteroaryl, CH<sub>2</sub>CH(R<sup>D</sup>)OR<sup>A</sup>, CH<sub>2</sub>CH(R<sup>D</sup>)NR<sup>A</sup>R<sup>B</sup>, and (CH<sub>2</sub>)<sub>m</sub>R<sup>C</sup>. In certain of such embodiments, the optionally substituted aryl or optionally substituted heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, CN, OR<sup>A</sup>, NO<sub>2</sub>, NR<sup>A</sup>R<sup>B</sup>, SR<sup>A</sup>, SOR<sup>A</sup>, SO<sub>2</sub>R<sup>A</sup>, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, and an optionally substituted C<sub>1</sub>-C<sub>4</sub> heteroalkyl.

[0129] In certain embodiments,  $R^{23}$  and  $R^{24}$  are each independently selected from hydrogen, an optionally substituted  $C_1$ - $C_8$  alkyl, an optionally substituted  $C_2$ - $C_8$  alkenyl, an optionally substituted  $C_1$ - $C_8$  haloalkyl, an optionally substituted  $C_2$ - $C_8$  haloalkenyl, an optionally substituted  $C_1$ - $C_8$  heteroalkyl, an optionally substituted  $C_2$ - $C_8$  heteroalkenyl, an optionally substituted  $C_2$ - $C_8$  alkynyl, an optionally substituted  $C_2$ - $C_8$  haloalkynyl, an optionally substituted  $C_2$ - $C_8$  heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl,  $CH(R^D)OR^A$ ,  $CH(R^D)NR^A R^B$ , and  $(CH_2)_m R^C$ . In certain embodiments,  $R^{23}$  and  $R^{24}$  together form a carbonyl group.

[0130] In certain embodiments,  $R^{22}$  and  $R^{23}$  are optionally linked to form a ring. In certain embodiments,  $R^{23}$  and  $R^{25}$  are optionally linked to form a ring.

[0131] In certain embodiments, X is selected from O, S,  $CR^A R^B$ ,  $NR^D$ , and a bond.

[0132] In certain embodiments, if X is  $CR^A R^B$  or a bond, then  $R^{25}$  and  $R^{26}$  are each independently selected from a halogen,  $OR^A$ ,  $NR^A R^B$ , hydrogen, an optionally substituted  $C_1$ - $C_8$  alkyl, an optionally substituted  $C_2$ - $C_8$  alkenyl, an optionally substituted  $C_1$ - $C_8$  haloalkyl, an optionally substituted  $C_2$ - $C_8$  haloalkenyl, an optionally substituted  $C_1$ - $C_8$  heteroalkyl, an optionally substituted  $C_2$ - $C_8$  heteroalkenyl, an optionally substituted  $C_2$ - $C_8$  alkynyl, an optionally substituted  $C_2$ - $C_8$  haloalkynyl, an optionally substituted  $C_2$ - $C_8$  heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, and  $(CH_2)_m R^C$ . In certain embodiments,  $R^{25}$  and  $R^{26}$  together form a carbonyl group.

[0133] In certain embodiments, if X is O, S, or  $\text{NR}^{\text{D}}$ , then  $\text{R}^{25}$  and  $\text{R}^{26}$  are each independently selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_8$  alkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkenyl, an optionally substituted  $\text{C}_1\text{-C}_8$  haloalkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  haloalkenyl, an optionally substituted  $\text{C}_1\text{-C}_8$  heteroalkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  heteroalkenyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkynyl, an optionally substituted  $\text{C}_2\text{-C}_8$  haloalkynyl, an optionally substituted  $\text{C}_2\text{-C}_8$  heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, and  $(\text{CH}_2)_m\text{R}^{\text{C}}$ . In certain embodiments  $\text{R}^{25}$  and  $\text{R}^{26}$  together form a carbonyl group.

[0134] In certain embodiments,  $\text{R}^{\text{A}}$  and  $\text{R}^{\text{B}}$  are each independently selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_4$  alkyl, an optionally substituted  $\text{C}_1\text{-C}_4$  haloalkyl, and an optionally substituted  $\text{C}_1\text{-C}_4$  heteroalkyl.

[0135] In certain embodiments,  $\text{R}^{\text{C}}$  is selected from an optionally substituted aryl and an optionally substituted heteroaryl that is optionally with a substituent selected from F, Cl, Br, I, CN,  $\text{OR}^{\text{A}}$ ,  $\text{NO}_2$ ,  $\text{NR}^{\text{A}}\text{R}^{\text{B}}$ ,  $\text{SR}^{\text{A}}$ ,  $\text{SOR}^{\text{A}}$ ,  $\text{SO}_2\text{R}^{\text{A}}$ , an optionally substituted  $\text{C}_1\text{-C}_4$  alkyl, an optionally substituted  $\text{C}_1\text{-C}_4$  haloalkyl, and an optionally substituted  $\text{C}_1\text{-C}_4$  heteroalkyl.

[0136] In certain embodiments,  $\text{R}^{\text{D}}$  is selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_4$  alkyl, an optionally substituted  $\text{C}_1\text{-C}_4$  haloalkyl, and an optionally substituted  $\text{C}_1\text{-C}_4$  heteroalkyl.

[0137] In certain embodiments, Z is selected from O, S,  $\text{CR}^{\text{A}}\text{R}^{\text{B}}$ , and  $\text{NR}^{\text{D}}$ .

[0138] In certain embodiments, n is 0, 1, or 2. In certain embodiments, m is 1

or 2.

[0139] In certain embodiments, if  $R^{18}$  is  $\text{NO}_2$  and X is O, then  $R^{19}$ ,  $R^{20}$ , and  $R^{21}$  are not each hydrogen. In certain embodiments, if  $R^{19}$  is  $\text{NO}_2$  and X is C, then at least one of  $R^{18}$ ,  $R^{20}$ , and  $R^{21}$  is not hydrogen. In certain embodiments, if  $R^{18}$  is  $\text{NO}_2$  and X is NH, then  $R^{23}$  and  $R^{24}$  do not together form a carbonyl.

[0140] In embodiments in which two or more of a particular variable are present, the identities of those two or more particular variables are selected independently and, thus, may be the same or different from one another. For example, certain compounds of the invention comprise two or more  $R^A$  groups. The identities of those two or more  $R^A$  groups are each selected independently. Thus, in certain embodiments, those  $R^A$  groups are all the same as one another; in certain embodiments, those  $R^A$  groups are all different from one another; and in certain embodiments, some of those  $R^A$  groups are the same as one another and some are different from one another.

[0141] In certain embodiments, a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, or Formula VI is a selective androgen receptor modulator. In certain embodiments, a compound of Formula I is a selective androgen receptor agonist. In certain embodiments, a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, or Formula VI is a selective androgen receptor antagonist. In certain embodiments, a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, or Formula VI is a selective androgen receptor partial agonist. In certain embodiments, a compound of Formula I, Formula II, Formula III, Formula IV, Formula

V, or Formula VI is a tissue-specific selective androgen modulator. In certain embodiments, a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, or Formula VI is a gene-specific selective androgen modulator. In certain embodiments, a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, or Formula VI is a selective androgen receptor binding compound.

[0142] In certain embodiments, the invention provides compounds selected from: N,N'-bis(2,2,2-trifluoroethyl)-3-methyl-4-nitroaniline; N,N'-bis(2,2,2-trifluoroethyl)-4-nitroaniline; 5-(2,2,2-trifluoroethyl)amino-2-bromobenzotrifluoride; 4-N,N'-bis(2,2,2-trifluoroethyl)amino-2-trifluoromethylbenzonitrile; (R)-N-4-nitrophenyl-5-(dimethyl-tert-butylsilyloxymethyl)-2-pyrrolidone; (R)-N-4-nitrophenyl-5-hydroxymethyl-2-pyrrolidone; (R)-N-(4-nitro-3-trifluoromethylphenyl)-2-dimethyl-tert-butylsilyloxymethylpyrrolidine; (R)-N-(4-nitro-3-trifluoromethylphenyl)-2-hydroxymethylpyrrolidine; (R)-N-(4-nitrophenyl)-2-hydroxymethylpyrrolidine; (R)-N-(3-Trifluoromethyl-4-nitrophenyl)-2-formylpyrrolidine; N-(3-Trifluoromethyl-4-nitrophenyl)-2-(R)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; N-(3-Trifluoromethyl-4-nitrophenyl)-2-(R)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; (S)-N-(4-nitrophenyl)-2-hydroxymethylpyrrolidine; N-(4-nitrophenyl)-2-(R)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; N-(4-nitrophenyl)-2-(R)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; and N-(4-nitrophenyl)-2-(S)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; and a pharmaceutically acceptable salt, ester, amide, or

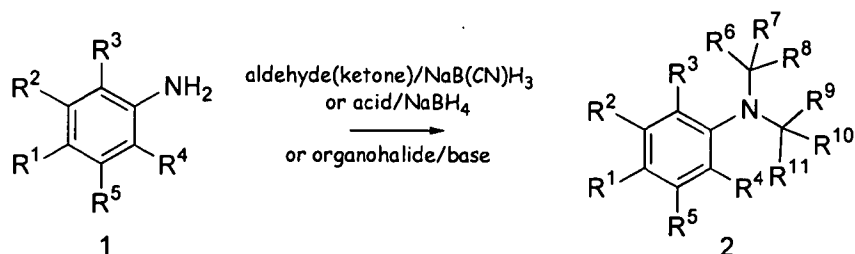
prodrug of any of those compounds.

[0143] Certain compounds of the present inventions may exist as stereoisomers including optical isomers. The present disclosure is intended to include all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are known in the art.

#### Certain Synthesis Methods

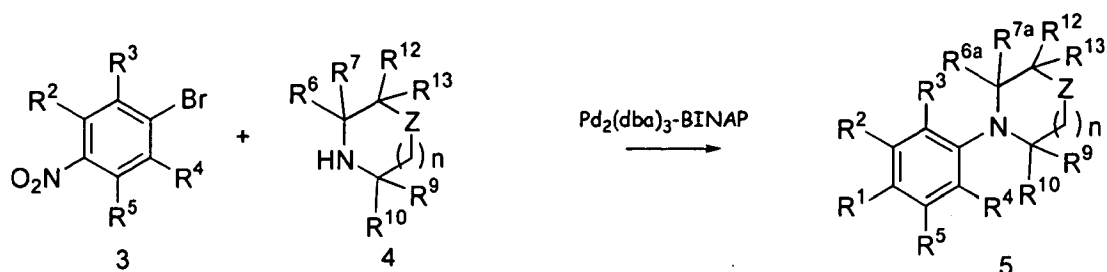
[0144] In certain embodiments, synthesis of compounds of the present invention is accomplished using the following synthesis schemes. In each of the Schemes the R groups correspond to the definitions described above.

#### Scheme I



[0145] Scheme I describes the alkylation of the substituted anilines such as Structure 1. Reductive alkylation of the substituted anilines (e.g., Structure 1) with an aldehyde or ketone or acid in the presence of a reducing agent, such as sodium cyanoborohydride or sodium borohydride affords compounds of Structure 2. Alternatively, treatment of the substituted anilines of Structure 1 with an organohalide in the presence of a base provides the compounds of Structure 2.

#### Scheme II



[0146] Scheme II describes the preparation of compounds of Structure 5 from the substituted aryl halides such as Structure 3. Palladium catalyzed coupling reaction of Structure 3 and compounds of Structure 4 provide the products of Structure 5.

[0147] In certain embodiments, the invention provides a salt corresponding to any of the compounds provided herein. In certain embodiments, the invention provides a salt corresponding to a selective androgen receptor modulator or selective androgen binding agent. In certain embodiments, a salt is obtained by reacting a compound with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. In certain embodiments, a salt is obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[0148] In certain embodiments, one or more carbon atoms of a compound of the present invention is replaced with silicon. *See e.g.*, WO 03/037905A1; Tacke and Zilch, Endeavour, New Series, 10, 191-197 (1986); Bains and Tacke, Curr. Opin. Drug

Discov Devel. Jul:6(4):526-43(2003). In certain embodiments, compounds of the present invention comprising one or more silicon atoms possess certain desired properties, including, but not limited to, greater stability and/or longer half-life in a patient, when compared to the same compound in which none of the carbon atoms have been replaced with a silicon atom.

#### Certain Assays

[0149] In certain embodiments, compounds of the present invention are capable of modulating activity of androgen receptors in a "co-transfection" assay (also called a "cis-trans" assay), which has been discussed previously. *See e.g.*, Evans *et al.*, *Science*, 240:889-95 (1988); U.S. Patent Nos. 4,981,784 and 5,071,773; Pathirana *et al.*, "Nonsteroidal Human Progesterone Receptor Modulators from the Marie Alga Cymopolia Barbata," *Mol. Pharm.* 47:630-35 (1995)). Modulating activity in a co-transfection assay has been shown to correlate with *in vivo* modulating activity. Thus, in certain embodiments, such assays are predictive of *in vivo* activity. *See, e.g.* Berger *et al.*, *J. Steroid Biochem. Molec. Biol.* 41:773 (1992).

[0150] In certain co-transfection assays, two different co-transfection plasmids are prepared. In the first co-transfection plasmid, cloned cDNA encoding an intracellular receptor (*e.g.*, androgen receptor) is operatively linked to a constitutive promoter (*e.g.*, the SV 40 promoter). In the second co-transfection plasmid, cDNA encoding a reporter protein, such as firefly luciferase (LUC), is operatively linked to a promoter that is activated by a receptor-dependant activation factor. Both co-

transfection plasmids are co-transfected into the same cells. Expression of the first co-transfection plasmid results in production of the intracellular receptor protein.

Activation of that intracellular receptor protein (*e.g.*, by binding of an agonist) results in production of a receptor-dependant activation factor for the promoter of the second co-transfection plasmid. That receptor-dependant activation factor in turn results in expression of the reporter protein encoded on the second co-transfection plasmid. Thus, reporter protein expression is linked to activation of the receptor. Typically, that reporter activity can be conveniently measured (*e.g.*, as increased luciferase production).

[0151] Certain co-transfection assays can be used to identify agonists, partial agonists, and/or antagonists of intracellular receptors. In certain embodiments, to identify agonists, co-transfected cells are exposed to a test compound. If the test compound is an agonist or partial agonist, reporter activity is expected to increase compared to co-transfected cells in the absence of the test compound. In certain embodiments, to identify antagonists, the cells are exposed to a known agonist (*e.g.*, androgen for the androgen receptor) in the presence and absence of a test compound. If the test compound is an antagonist, reporter activity is expected to decrease relative to that of cells exposed only to the known agonist.

[0152] In certain embodiments, compounds of the invention are used to detect the presence, quantity and/or state of receptors in a sample. In certain of such embodiments, samples are obtained from a patient. In certain embodiments,

compounds are radio- or isotopically-labeled. For example, compounds of the present invention that selectively bind androgen receptors may be used to determine the presence of such receptors in a sample, such as cell homogenates and lysates.

Certain Pharmaceutical Agents

[0153] In certain embodiments, at least one selective androgen receptor modulator, or pharmaceutically acceptable salt, ester, amide, and/or prodrug thereof, either alone or combined with one or more pharmaceutically acceptable carriers, forms a pharmaceutical agent. Techniques for formulation and administration of compounds of the present invention may be found for example, in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

[0154] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is prepared using known techniques, including, but not limited to mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[0155] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is a liquid (*e.g.*, a suspension, elixir and/or solution). In certain of such embodiments, a liquid pharmaceutical agent comprising one or more compounds of the present invention is prepared using ingredients known in the art, including, but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents.

[0156] In certain embodiments, a pharmaceutical agent comprising one or more

compounds of the present invention is a solid (*e.g.*, a powder, tablet, and/or capsule). In certain of such embodiments, a solid pharmaceutical agent comprising one or more compounds of the present invention is prepared using ingredients known in the art, including, but not limited to, starches, sugars, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0157] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is formulated as a depot preparation. Certain of such depot preparations are typically longer acting than non-depot preparations. In certain embodiments, such preparations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, depot preparations are prepared using suitable polymeric or hydrophobic materials (for example an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0158] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical agents including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

[0159] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises one or more tissue-specific delivery

molecules designed to deliver the pharmaceutical agent to specific tissues or cell types. For example, in certain embodiments, pharmaceutical agents include liposomes coated with a tissue-specific antibody.

[0160] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0161] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a sustained-release system. A non-limiting example of such a sustained-release system is a semipermeable matrix of solid hydrophobic polymers. In certain embodiments, sustained-release systems may,

depending on their chemical nature, release compounds over a period of hours, days, weeks or months.

[0162] Certain compounds used in pharmaceutical agent of the present invention may be provided as pharmaceutically acceptable salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, *etc.*

[0163] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises an active ingredient in a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

[0164] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is formulated as a prodrug. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (*e.g.*, through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, a prodrug is an ester. In certain embodiments, such prodrugs are less water soluble than the corresponding active form.

In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, the ester in such prodrugs is metabolically hydrolyzed to carboxylic acid. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a prodrug comprises a short peptide (polyaminoacid) bound to an acid group. In certain of such embodiments, the peptide is metabolized to form the corresponding active form.

[0165] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is useful for treating a conditions or disorder in a mammalian, and particularly in a human patient. Suitable administration routes include, but are not limited to, oral, rectal, transmucosal, intestinal, enteral, topical, suppository, through inhalation, intrathecal, intraventricular, intraperitoneal, intranasal, intraocular and parenteral (*e.g.*, intravenous, intramuscular, intramedullary, and subcutaneous). In certain embodiments, pharmaceutical intrathecal are administered to achieve local rather than systemic exposures. For example, pharmaceutical agents may be injected directly in the area of desired effect (*e.g.*, in the renal or cardiac area).

[0166] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is administered in the form of a dosage unit (*e.g.*, tablet, capsule, bolus, etc.). In certain embodiments, such dosage units comprise a selective androgen receptor modulator in a dose from about 1  $\mu\text{g/kg}$  of body weight to about 50  $\text{mg/kg}$  of body weight. In certain embodiments, such dosage units comprise a

selective androgen receptor modulator in a dose from about 2  $\mu\text{g/kg}$  of body weight to about 25 mg/kg of body weight. In certain embodiments, such dosage units comprise a selective androgen receptor modulator in a dose from about 10  $\mu\text{g/kg}$  of body weight to about 5 mg/kg of body weight. In certain embodiments, pharmaceutical agents are administered as needed, once per day, twice per day, three times per day, or four or more times per day. It is recognized by those skilled in the art that the particular dose, frequency, and duration of administration depends on a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the pharmaceutical agent.

[0167] In certain embodiments, a pharmaceutical agent comprising a compound of the present invention is prepared for oral administration. In certain of such embodiments, a pharmaceutical agent is formulated by combining one or more compounds of the present invention with one or more pharmaceutically acceptable carriers. Certain of such carriers enable compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. In certain embodiments, pharmaceutical agents for oral use are obtained by mixing one or more compounds of the present invention and one or more solid excipient. Suitable excipients include, but are not limited to, fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium

carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). In certain embodiments, such a mixture is optionally ground and auxiliaries are optionally added. In certain embodiments, pharmaceutical agents are formed to obtain tablets or dragee cores. In certain embodiments, disintegrating agents (*e.g.*, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate) are added.

[0168] In certain embodiments, dragee cores are provided with coatings. In certain of such embodiments, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings.

[0169] In certain embodiments, pharmaceutical agents for oral administration are push-fit capsules made of gelatin. Certain of such push-fit capsules comprise one or more compounds of the present invention in admixture with one or more filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, pharmaceutical agents for oral administration are soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In certain soft capsules, one or more compounds of the present invention are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

[0170] In certain embodiments, pharmaceutical agents are prepared for buccal administration. Certain of such pharmaceutical agents are tablets or lozenges

formulated in conventional manner.

[0171] In certain embodiments, a pharmaceutical agent is prepared for administration by injection (*e.g.*, intravenous, subcutaneous, intramuscular, etc.). In certain of such embodiments, a pharmaceutical agent comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (*e.g.*, ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical agents for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers. Certain pharmaceutical agents for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical agents for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0172] In certain embodiments, a pharmaceutical agent is prepared for

transmucosal administration. In certain of such embodiments penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0173] In certain embodiments, a pharmaceutical agent is prepared for administration by inhalation. Certain of such pharmaceutical agents for inhalation are prepared in the form of an aerosol spray in a pressurized pack or a nebulizer. Certain of such pharmaceutical agents comprise a propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain embodiments using a pressurized aerosol, the dosage unit may be determined with a valve that delivers a metered amount. In certain embodiments, capsules and cartridges for use in an inhaler or insufflator may be formulated. Certain of such formulations comprise a powder mixture of a compound of the invention and a suitable powder base such as lactose or starch.

[0174] In certain embodiments, a pharmaceutical agent is prepared for rectal administration, such as a suppositories or retention enema. Certain of such pharmaceutical agents comprise known ingredients, such as cocoa butter and/or other glycerides.

[0175] In certain embodiments, a pharmaceutical agent is prepared for topical administration. Certain of such pharmaceutical agents comprise bland moisturizing bases, such as ointments or creams. Exemplary suitable ointment bases include, but are not limited to, petrolatum, petrolatum plus volatile silicones, lanolin and water in oil

emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Exemplary suitable cream bases include, but are not limited to, Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Pfizer (Morris Plains, New Jersey).

[0176] In certain embodiments, the formulation, route of administration and dosage for a pharmaceutical agent of the present invention can be chosen in view of a particular patient's condition. (See e.g., Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). In certain embodiments, a pharmaceutical agent is administered as a single dose. In certain embodiments, a pharmaceutical agent is administered as a series of two or more doses administered over one or more days.

[0177] In certain embodiments, a pharmaceutical agent of the present invention is administered to a patient between about 0.1% and 500%, more preferably between about 25% and 75% of an established human dosage. Where no human dosage is established, a suitable human dosage may be inferred from ED<sub>50</sub> or ID<sub>50</sub> values, or other appropriate values derived from *in vitro* or *in vivo* studies.

[0178] In certain embodiments, a daily dosage regimen for a patient comprises an oral dose of between 0.1 mg and 2000 mg of a compound of the present invention. In certain embodiments, a daily dosage regimen is administered as a single daily dose. In certain embodiments, a daily dosage regimen is administered as two, three, four, or more than four doses.

[0179] In certain embodiments, a pharmaceutical agent of the present invention is administered by continuous intravenous infusion. In certain of such embodiments, from 0.1 mg to 500 mg of a composition of the present invention is administered per day.

[0180] In certain embodiments, a pharmaceutical agent of the invention is administered for a period of continuous therapy. For example, a pharmaceutical agent of the present invention may be administered over a period of days, weeks, months, or years.

[0181] Dosage amount, interval between doses, and duration of treatment may be adjusted to achieve a desired effect. In certain embodiments, dosage amount and interval between doses are adjusted to maintain a desired concentration of compound in a patient. For example, in certain embodiments, dosage amount and interval between doses are adjusted to provide plasma concentration of a compound of the present invention at an amount sufficient to achieve a desired effect. In certain of such embodiments the plasma concentration is maintained above the minimal effective concentration (MEC). In certain embodiments, pharmaceutical agents of the present invention are administered with a dosage regimen designed to maintain a concentration above the MEC for 10-90% of the time, between 30-90% of the time, or between 50-90% of the time.

[0182] In certain embodiments in which a pharmaceutical agent is administered locally, the dosage regimen is adjusted to achieve a desired local concentration of a

compound of the present invention.

[0183] In certain embodiments, a pharmaceutical agent may be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0184] In certain embodiments, a pharmaceutical agent is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

#### Certain Combination Therapies

[0185] In certain embodiments, one or more pharmaceutical agents of the present invention are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical agents of the

present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical agents of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical agents of the present invention. In certain embodiments, one or more pharmaceutical agents of the present invention is co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are administered at the different times. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are prepared separately.

[0186] Examples of pharmaceutical agents that may be co-administered with a pharmaceutical agent of the present invention include, but are not limited to, analgesics (*e.g.*, acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (*e.g.*, ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (*e.g.*, biguanides, glucosidase inhibitors, insulins, sulfonylureas, and

thiazolidinediones); adrenergic modifiers; diuretics; hormones (*e.g.*, anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostatin, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (*e.g.*, biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

#### Certain Indications

[0187] In certain embodiments, the invention provides methods of treating a patient comprising administering one or more compounds of the present invention. In certain embodiments, such patient suffers from an androgen receptor mediated condition. In certain embodiments, a patient is treated prophylactically to reduce or prevent the occurrence of a condition.

[0188] Exemplary conditions that may be treated with one or more compounds of the present invention included, but are not limited to, acne, male-pattern baldness, wasting diseases, hirsutism, hypogonadism, osteoporoses, infertility, impotence, obesity, and cancer. In certain embodiments, one or more compounds of the present invention are used to stimulate hematopoiesis. In certain embodiments, one or more compounds of the present invention are used for contraception.

[0189] In certain embodiments, one or more compounds of the present invention are used to treat cancer. Certain exemplary cancers include, but are not limited to, breast cancer, colorectal cancer, gastric carcinoma, glioma, head and neck squamous

cell carcinoma, papillary renal carcinoma, leukemia, lymphoma, Li-Fraumeni syndrome, malignant pleural mesothelioma, melanoma, multiple myeloma, non-small cell lung cancer, synovial sarcoma, thyroid carcinoma, transitional cell carcinoma of urinary bladder, and prostate cancer, including, but not limited to prostatic hyperplasia.

[0190] In certain embodiments, one or more compounds of the present invention are used to improve athletic performance. In certain such embodiments, one or more compounds of the present invention are used, for example to shorten the time normally needed to recover from physical exertion or to increase muscle strength. Athletes to whom one or more compounds of the present invention may be administered include, but are not limited to, horses, dogs, and humans. In certain embodiments, one or more compounds of the present invention are administered to an athlete engaged in a professional or recreational competition, including, but not limited to weight-lifting, body-building, track and field events, and any of various team sports.

[0191] In certain embodiments, the invention provides methods for treating a patient comprising administering one or more selective androgen receptor agonists and/or partial agonists. Exemplary conditions that may be treated with such selective androgen receptor agonists and/or partial agonist include, but are not limited to, hypogonadism, wasting diseases, cancer cachexia, frailty, infertility, and osteoporosis. In certain embodiments, a selective androgen receptor agonist or partial agonist is used for male hormone replacement therapy. In certain embodiments, one or more selective androgen receptor agonists and/or partial agonists are used to stimulate hematopoiesis.

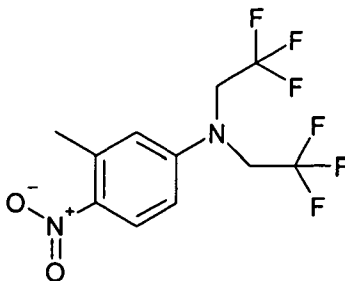
In certain embodiments, a selective androgen receptor agonist or partial agonist is used as an anabolic agent. In certain embodiments, a selective androgen receptor agonist and/or partial agonist is used to improve athletic performance.

[0192] In certain embodiments, the invention provides methods for treating a patient comprising administering one or more selective androgen receptor antagonists and/or partial agonists. Exemplary conditions that may be treated with such one or more selective androgen receptor antagonists and/or partial agonists include, but are not limited to, hirsutism, acne, male-pattern baldness, prostatic hyperplasia, and cancer, including, but not limited to, various hormone-dependent cancers, including, without limitation, prostate and breast cancer.

#### Examples

[0193] The following examples, including experiments and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

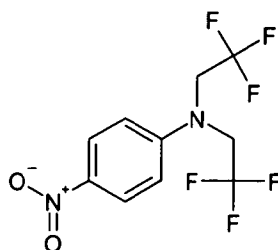
#### Example 1



N,N'-bis(2,2,2-trifluoroethyl)-3-methyl-4-nitroaniline (Compound 101, Structure 2 of Scheme I, where  $R^1 = \text{NO}_2$ ,  $R^2 = \text{CH}_3$ ,  $R^3 = R^4 = R^5 = R^6 = R^7 = R^{10} = R^{11} = \text{H}$ ,  $R^8 = R^9 = \text{CF}_3$ )

[0194] To prepare this compound, first 3.9g (25 mmol) of 3-methyl-4-nitroaniline was dissolved in 100mL of trifluoroacetic acid with stirring under  $\text{N}_2$  at 60°C. Next, sodium borohydride pellets (14 g, 15eq) were added portionwise. Ten minutes after addition of the pellets, the reaction was heated to 90°C. After 12h at 90°C, the reaction was cooled, added slowly to water, and then filtered. The resulting solid filtrate was washed first with water and then with hexanes and was then dried. This procedure resulted in 6.6g (82% yield) of a light yellow powder. Data for compound 101:  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500MHz) 8.10 (d, 1H,  $J = 9.3$  Hz), 6.78 (dd, 1H,  $J = 9.3$  and 2.9 Hz), 6.72 (d, 1H,  $J = 2.9$  Hz), 4.13 (q, 4H,  $J = 8.4$  Hz), 2.66 (s, 3H).

## Example 2

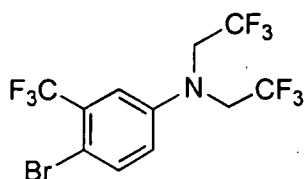


N,N'-bis(2,2,2-trifluoroethyl)-4-nitroaniline ((Compound 102, Structure 2 of Scheme I, where  $R^1 = \text{NO}_2$ ,  $R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = R^{10} = R^{11} = \text{H}$ ,  $R^8 = R^9 = \text{CF}_3$ )

[0195] This compound was prepared using the method described in Example 1, except that 4-nitroaniline was used in place of 3-methyl-4-nitroaniline. Compound 102 was isolated as a solid:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400MHz) 8.19 (d, 2H,  $J = 9.5$  Hz), 8.6.93 (d,

2H,  $J = 9.5\text{Hz}$ ), 4.16 (q, 2H,  $J = 8.3\text{Hz}$ ).

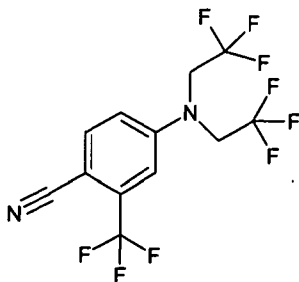
**Example 3A**



5-(2,2,2-trifluoroethyl)amino-2-bromobenzotrifluoride (Compound 103A, Structure 2 of Scheme I, where  $R^1 = \text{bromo}$ ,  $R^2 = \text{trifluoromethyl}$ ;  $R^3 = R^4 = R^5 = R^6 = R^7 = R^{10} = R^{11} = \text{H}$ ,  $R^8 = R^9 = \text{CF}_3$ )

[0196] This compound was prepared using the method described in Example 1, except that 5-amino-2-bromobenzotrifluoride was used in place of 3-methyl-4-nitroaniline. Compound 103A was isolated as a solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 7.58 (d, 1H,  $J = 8.8\text{ Hz}$ ), 7.19 (d, 1H,  $J = 3.2\text{ Hz}$ ), 6.91 (dd, 1H,  $J = 8.8$  and  $3.2\text{ Hz}$ ), 4.06 (q, 4H,  $J = 8.5\text{ Hz}$ ).

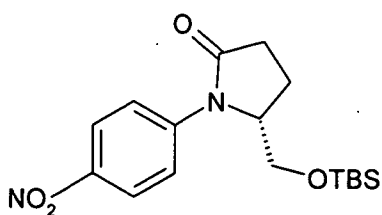
**Example 3**



4-N,N'-bis(2,2,2-trifluoroethyl)amino-2-trifluoromethylbenzonitrile (Compound 103, Structure 2 of Scheme I, where  $R^1 = \text{cyano}$ ,  $R^2 = \text{trifluoromethyl}$ ;  $R^3 = R^4 = R^5 = R^6 = R^7 = R^{10} = R^{11} = \text{H}$ ,  $R^8 = R^9 = \text{CF}_3$ )

[0197] To prepare this compound,  $\text{Zn}(\text{CN})_2$  (26 mg, 0.22 mmol),  $\text{Pd}(\text{PPh}_3)_4$ , and Compound 103A (77 mg, 0.19 mmol) were combined in a dry Schenck flask. That mixture was then added to 2 ml of a 1% DMF/water solution, which had been degassed by bubbling  $\text{N}_2$  for 20 min. That mixture was then heated to 130 °C for 20 h, and then partitioned with EtOAc and saturated  $\text{NH}_4\text{Cl}$ . The organic layer was washed sequentially with water and then with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated. Flash chromatography (4:1 hexanes:EtOAc) afforded Compound 103. Compound 103 was isolated as a solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 7.73 (d, 1H,  $J = 8.8$  Hz), 7.19 (d, 1H,  $J = 2.8$  Hz), 7.08 (dd, 1H,  $J = 8.8$  and 2.8 Hz), 4.16 (q, 4H,  $J = 8.2$  Hz).

#### **Example 4**



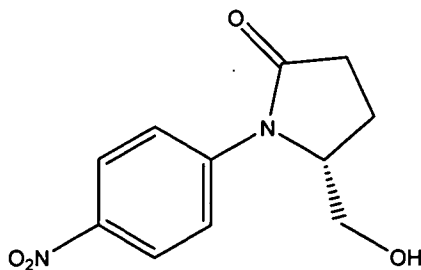
(R)-N-4-nitrophenyl-5-(dimethyl-tert-butylsilyloxymethyl)-2-pyrrolidone (Compound 104, Structure 5 of Scheme II, where  $\text{R}^1 = \text{nitro}$ ,  $\text{R}^{10} = \text{dimethyl-tert-butylsilyloxymethyl}$ ,  $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{R}^9 = \text{R}^{12} = \text{R}^{13} = \text{H}$ ,  $\text{R}^{6a}$  and  $\text{R}^{7a}$  form a carbonyl,  $n = 1$ ,  $Z = \text{a bond}$ )

[0198] This compound was prepared using General Procedure I (Palladium mediated coupling of aryl bromide and alkylamine) in which a solution of an aryl

bromide (such as 4-nitroaniline in toluene (0.05-0.2 M)),  $\text{Cs}_2\text{CO}_3$  (2-3 equiv),  $\text{Pd}2(\text{dba})_3$  (1-3 mol %), and (R)-BINAP (2.0 mg, 0.003 mmol, 1.5-4.5 mol%) are combined in a schlenk tube. Then an amine or amide (3-5 equiv) is added. The resulting reaction mixture is heated to 100 °C for 4-48 hours, cooled to room temperature, diluted with  $\text{Et}_2\text{O}$ , filtered, and concentrated in vacuo. Chromatography ( $\text{CH}_2\text{Cl}_2$ :hexane or  $\text{EtOAc}$ :hexane mixtures) of the crude mixture afforded compounds of Structure 5.

[0199] Compound 104 was prepared according the General Procedure I using 4-bromonitrobenzene as the aryl bromide. Compound 104 was isolated as a yellow oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 8.1 (s, 1H), 8.0 (m, 2H), 4.5 (m, 1H), 3.76 (dd, 1H,  $J = 3.9$  and 10.7Hz), 3.70 (dd, 1H,  $J = 3.4$  and 10.7Hz), 2.8 (m, 1H), 2.6 (m, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 0.8 (s, 9H), 0.1 (s, 3H), 0.0 (s, 3H).

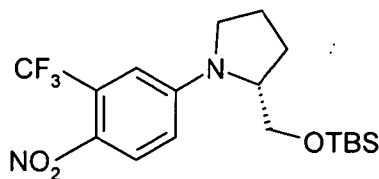
### Example 5



(R)-N-4-nitrophenyl-5-hydroxymethyl-2-pyrrolidone (Compound 105, Structure 5 of Scheme II, where  $\text{R}^1 = \text{nitro}$ ,  $\text{R}^{10} = \text{hydroxymethyl}$ ,  $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{R}^9 = \text{R}^{12} = \text{R}^{13} = \text{H}$ ,  $\text{R}^{6a}$  and  $\text{R}^{7a}$  form a carbonyl,  $n = 1$ ,  $Z = \text{a bond}$ )

[0200] Compound 105 was prepared by hydrolyzing the silyl group of Compound 104. Compound 105 was isolated as an oil:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 8.25 (d, 2H,  $J = 9.3$  Hz), 7.77 (d, 2H,  $J = 9.3$  Hz), 4.48 (ddt, 1H,  $J = 8.6$ , 4.6 and 3.0 Hz), 3.82 (dt, 1H,  $J = 11.4$  and 4.6 Hz), 3.74 (ddd, 1H,  $J = 11.4$ , 5.5 and 3.0 Hz), 2.81 (ddd, 1H,  $J = 17.5$ , 10.0 and 8.6 Hz), 2.58 (ddd, 1H,  $J = 17.5$ , 10.1 and 4.3 Hz), 2.36 (ddt, 1H,  $J = 13.0$ , 10.1 and 8.6 Hz), 2.22 (dddd, 1H,  $J = 13.0$ , 10.0, 4.3 and 3.0 Hz), 1.61 (dd, 1H,  $J = 5.5$  and 4.6 Hz).

### Example 6

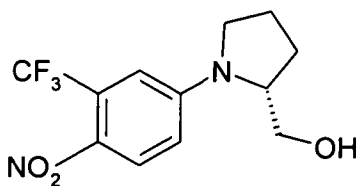


(R)-N-(4-nitro-3-trifluoromethylphenyl)-2-dimethyl-tert-butylsilyloxymethylpyrrolidine  
(Compound 106, Structure 5 of Scheme II, where  $\text{R}^1 = \text{nitro}$ ,  $\text{R}^2 = \text{trifluoromethyl}$ ,  $\text{R}^{10} =$   
dimethyl-tert-butylsilyloxymethyl,  $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{R}^{6a} = \text{R}^{7a} = \text{R}^9 = \text{R}^{12} = \text{R}^{13} = \text{H}$ ,  $n = 1$ ,  
 $\text{Z} = \text{a bond}$ )

[0201] To prepare this compound, first (R)-N-(4-nitro-3-trifluoromethylphenyl)-2-dimethyl-tert-butylsilyloxymethyl-2-pyrrolidone (Compound 107, Structure 5 of Scheme II, where  $\text{R}^1 = \text{nitro}$ ,  $\text{R}^2 = \text{trifluoromethyl}$ ,  $\text{R}^{10} = \text{dimethyl-tert-butylsilyloxymethyl}$ ,  $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{R}^9 = \text{R}^{12} = \text{R}^{13} = \text{H}$ ,  $\text{R}^{6a}$  and  $\text{R}^{7a}$  form a carbonyl,  $n = 1$ ,  $\text{Z} = \text{a bond}$ ) was prepared using the method described in Example 4, except that 3-

trifluoromethyl-4-nitrobromobenzene was used in place of 4-nitrobromobenzene. That Compound 107 (1.94g, 4.6mmol) was dissolved in 3mL of dry THF with stirring and then cooled in an ice water bath. An Alane/dimethylethylamine complex (36mL, 18mmol) was added and the mixture was allowed to warm to room temperature. After 1 hour, 50mL of methanol and 4mL of glacial acetic acid were added, followed by addition of sodiumcyanoborohydride (2.89g, 46mmol). After 10 minutes, the reaction mixture was concentrated under reduced pressure. Water was added and the solution was extracted with EtOAc. The extracted organic layer was washed with saturated NaHCO<sub>3</sub> and Brine (2X), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. Chromatography (silica, 50% EtOAc : Hex) afforded 624mg (41% pure) yellow oil. Data for Compound 106: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) 8.10 (d, 1H, J=9.27), 6.99 (d, 1H, J=2.44Hz), 6.72 (dd, 1H, J=2.93 and 9.27Hz), 4.05 (m, 1H), 3.70 (dd, 1H, J=4.88 and 10.25Hz), 3.63 (dd, 1H, J=6.34 and 10.25Hz), 3.55 (m, 1H), 3.35 (m, 1H), 2.0-2.2 (m, 4H), 0.9 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). LCMS 404 (M<sup>+</sup>), 259 (M<sup>+</sup>-CH<sub>2</sub>OTBS, 100%).

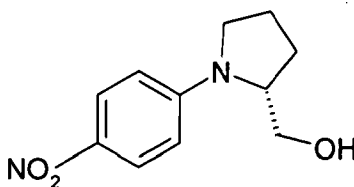
**Example 7**



(R)-N-(4-nitro-3-trifluoromethylphenyl)-2-hydroxymethylpyrrolidine (Compound 108, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^2$  = trifluoromethyl,  $R^{10}$  = hydroxymethyl,  $R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z = a$  bond)

[0202] Compound 106 from Example 6 (620mg, 1.53mmol) was dissolved in 4mL of ethanol with stirring, 1mL of  $CHCl_3$  was added at room temperature. After the reaction was judged complete by TLC (40% EtOAc/Hex) the pH was adjusted to ~8 using 1N NaOH. The mixture was extracted with EtOAc and the organic layer was washed with Brine, dried ( $MgSO_4$ ) and concentrated under reduced pressure. The resulting oil was triturated with hexanes, decanted and dried to afford a yellow oil (354mg, 79% pure). Data for Compound 108:  $^1H$  NMR ( $CDCl_3$ , 400MHz) 8.08 (d, 1H,  $J = 9.27Hz$ ), 7.0 (d, 1H,  $J = 2.44Hz$ ), 6.77 (dd, 1H,  $J = 2.44$  and  $9.27Hz$ ), 4.09 (m, 1H), 3.77 (m, 1H), 3.71 (m, 1H), 3.62 (m, 1H), 3.36 (m, 1H), 2.1-2.2 (m, 4H), and 1.63 (m, 1H).

### Example 8

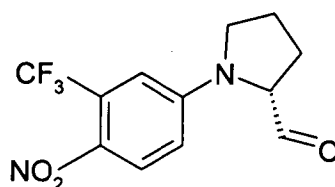


(R)-N-(4-nitrophenyl)-2-hydroxymethylpyrrolidine (Compound 109, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^{10}$  = hydroxymethyl,  $R^2 = R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z = a$  bond)

[0203] This compound was prepared by reduction of the carbonyl group of

Compound 105 using the same reaction described in Example 7, except that compound 105 was used as the starting material in place of compound 106. Data for Compound 109:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 8.16 (m, 2H), 6.65 (m, 2H), 4.06 (m, 1H), 3.78 (m, 1H), 3.68 (m, 1H), 3.59 (m, 1H), 3.35 (m, 1H), 2.1-2.2 (m, 4H), 1.6 (m, 1H).

### Example 9

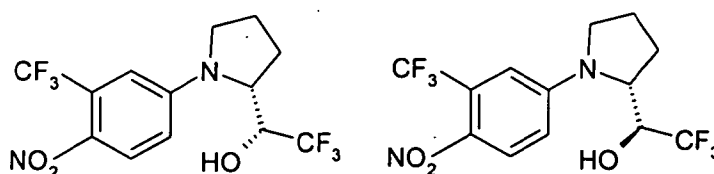


(R)-N-(3-Trifluoromethyl-4-nitrophenyl)-2-formylpyrrolidine (Compound 110,

Structure 5 of Scheme II, where  $\text{R}^1 = \text{nitro}$ ,  $\text{R}^2 = \text{trifluoromethyl}$ ,  $\text{R}^{10} = \text{formyl}$ ,  $\text{R}^3 = \text{R}^4 = \text{R}^5 = \text{R}^{6a} = \text{R}^{7a} = \text{R}^9 = \text{R}^{12} = \text{R}^{13} = \text{H}$ ,  $n = 1$ ,  $Z = \text{a bond}$ )

[0204] This compound was prepared by oxidation of Compound 108 from Example 7. Data for Compound 110:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 9.63 (d, 1H,  $J = 2.44\text{Hz}$ ), 8.08 (d, 1H,  $J = 9.27\text{Hz}$ ), 6.89 (d, 1H,  $J = 2.44\text{Hz}$ ), 6.65 (dd, 1H,  $J = 2.44$  and  $9.27\text{Hz}$ ), 4.38 (m, 1H), 3.75 (m, 1H), 3.56 (m, 1H), 2.37 (m, 2H), 2.23 (m, 1H), 2.1 (m, 1H).

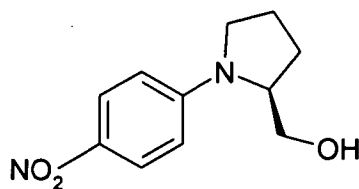
### Example 10



N-(3-Trifluoromethyl-4-nitrophenyl)-2-(R)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine (Compound 111, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^2$  = trifluoromethyl,  $R^{10}$  = 1-(S)-hydroxy-2,2,2-trifluoroethyl,  $R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z$  = a bond) and N-(3-Trifluoromethyl-4-nitrophenyl)-2-(R)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine (Compound 112, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^2$  = trifluoromethyl,  $R^{10}$  = 1-(R)-hydroxy-2,2,2-trifluoroethyl,  $R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z$  = a bond)

[0205] To prepare these compounds, compound 110 from Example 9 (290mg, 1.01mmol) was dissolved in 8mL of dry THF and cooled in isopropanol/acetone bath with stirring. Cesium fluoride (760mg, 5mmol) and  $TMSCF_3$  (163 $\mu$ L, 1.1mmol) were added and the reaction was allowed to warm to room temperature. After 12 hours, water was added and the mixture was extracted into EtOAc, dried ( $MgSO_4$ ) and concentrated under reduced pressure. Chromatography (silica, 35-40% gradient EtOAc : Hex) afforded the separated diastereoisomers. Data for Compound 111:  $^1H$  NMR ( $CDCl_3$ , 400MHz) 8.10 (d, 1H,  $J = 9.27Hz$ ), 6.95 (d, 1H,  $J = 2.92Hz$ ), 6.69 (dd, 1H,  $J = 2.92$  and  $9.27Hz$ ), 4.39 (m, 1H), 4.28 (m, 1H), 3.69 (m, 1H), 3.43 (m, 1H), 2.54 (m, 1H), 2.4 (m, 2H), 2.12 (m, 2H). Data for Compound 112:  $^1H$  NMR ( $CDCl_3$ , 400MHz) isomer 2: 8.06 (d, 1H,  $J = 9.27Hz$ ), 7.15 (d, 1H,  $J = 2.92Hz$ ), 6.93 (dd, 1H,  $J = 2.92$  and  $9.27Hz$ ), 4.32 (m, 1H), 3.98 (m, 1H), 3.60 (m, 1H), 3.37 (m, 1H), 2.50 (d, 1H,  $J = 3.9Hz$ ), 2.1-2.3 (m, 4H).

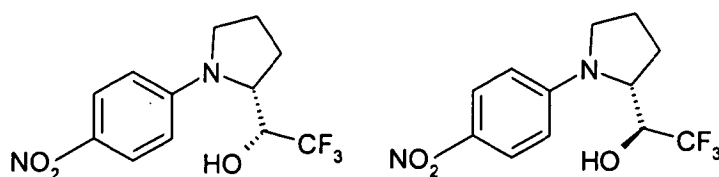
### **Example 11**



(S)-N-(4-nitrophenyl)-2-hydroxymethylpyrrolidine (Compound 113, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^{10}$  = hydroxymethyl,  $R^2 = R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z$  = a bond)

[0206] This compound was prepared using the method described in Example 8, except that the S-isomer of Compound 105 was used as the starting material. Data for Compound 113:  $^1H$  NMR ( $CDCl_3$ , 500MHz) 8.08 (d, 2H,  $J = 9.5$  Hz), 6.60 (d, 2H,  $J = 9.5$  Hz), 4.02 (m, 1H), 3.73 (ddd, 1H,  $J = 11.0, 5.7$  and  $4.2$  Hz), 3.64 (ddd, 1H,  $J = 11.0, 7.0$  and  $5.7$  Hz), 3.55 (m, 1H), 3.30 (dt, 1H,  $J = 10.3$  and  $7.8$  Hz), 2.11 (m, 4H), 1.73 (t, 1H,  $J = 5.7$  Hz).

### Example 12

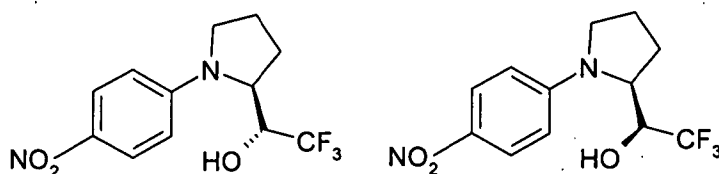


N-(4-nitrophenyl)-2-(R)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine (Compound 114, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^{10}$  = 1-(S)-hydroxy-2,2,2-trifluoroethyl,  $R^2 = R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z$  = a bond)  
and N-(4-nitrophenyl)-2-(R)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine

(Compound 115, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^{10}$  = 1-(R)-hydroxy-2,2,2-trifluoroethyl,  $R^2 = R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z = \text{a bond}$ )

[0207] To prepare these compounds, first Compound 109 was oxidized using the method described Example 9 except that Compound 109 was used in place of Compound 108. The resulting compound was then used in place of Compound 110 in the method described in Example 10. Data for Compound 114:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 8.14 (m, 2H), 6.57 (m, 2H), 4.45 (m, 1H), 4.26 (m, 1H), 3.68 (m, 1H), 3.41 (m, 1H), 2.53 (d, 1H,  $J = 5.37\text{Hz}$ ), 2.45 (m, 1H), 2.38 (m, 1H), 2.0-2.2 (m, 2H). Data for Compound 115:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 8.16 (m, 2H), 6.85 (m, 2H), 4.35 (m, 1H), 3.95 (m, 1H), 3.68 (m, 1H), 3.36 (m, 1H), 2.56 (br s, 1H), 2.24 (m, 1H), 2.1-2.2 (m, 3H).

### Example 13



N-(4-nitrophenyl)-2-(S)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine (Compound

116, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^{10}$  = 1-(S)-hydroxy-2,2,2-

trifluoroethyl,  $R^2 = R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z = \text{a bond}$ )

and N-(4-nitrophenyl)-2-(S)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine

(Compound 117, Structure 5 of Scheme II, where  $R^1$  = nitro,  $R^{10}$  = 1-(R)-hydroxy-2,2,2-

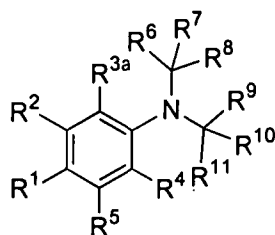
trifluoroethyl,  $R^2 = R^3 = R^4 = R^5 = R^{6a} = R^{7a} = R^9 = R^{12} = R^{13} = H$ ,  $n = 1$ ,  $Z = \text{a bond}$ )

[0208] To prepare these compounds, first Compound 113 was oxidized using the method described Example 9 except that Compound 113 was used in place of Compound 108. The resulting compound was then used in place of Compound 110 in the method described in Example 10. Data for Compound 116:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 8.09 (m, 2H), 6.75 (m, 2H), 4.46 (m, 1H), 4.26 (br d, 1H,  $J = 7.32\text{Hz}$ ), 3.66 (m, 1H), 3.45 (m, 1H), 2.70 (d, 1H,  $J = 5.37\text{Hz}$ ), 2.55 (m, 1H), 2.38 (m, 1H), 2.0-2.15 (m, 2H). Data for Compound 117:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400MHz) 8.16 (m, 2H), 6.85 (m, 2H), 4.35 (m, 1H), 3.95 (m, 1H), 3.68 (m, 1H), 3.36 (m, 1H), 2.55 (d, 1H,  $J = 3.90\text{Hz}$ ), 2.24 (m, 1H), 2.1-2.2 (m, 3H).

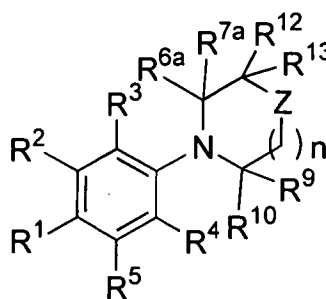
[0209] While description of the preferred embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Various modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

WHAT IS CLAIMED IS:

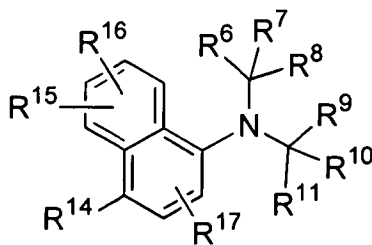
1. A compound having a structure selected from Formula I, Formula II, Formula III, Formula IV, Formula V, and Formula VI:



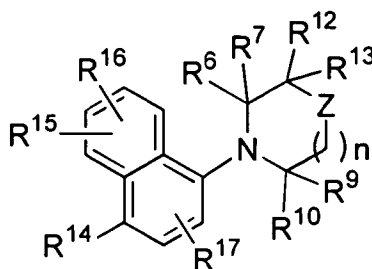
(I)



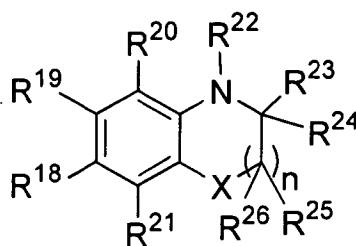
(II)



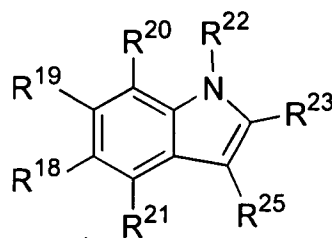
(III)



(IV)



(V)



(VI)

wherein:

$R^1$  and  $R^2$  are each independently selected from hydrogen, F, Cl, Br, I,  $OR^A$ ,  $SR^A$ ,  $NO_2$ , CN, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, an optionally substituted  $C_1$ - $C_4$  heteroalkyl,  $COR^A$ ,  $CO_2R^A$ ,  $CONR^AR^B$ ,

$\text{SOR}^A$ ,  $\text{SO}_2\text{R}^A$ , and  $\text{SO}_2\text{NR}^A\text{R}^B$ ,  $\text{NHCOR}^A$ , and  $\text{NHCONR}^A\text{R}^B$ , provided that at least one of  $\text{R}^1$  and  $\text{R}^2$  is not hydrogen;

$\text{R}^3$ ,  $\text{R}^{3a}$ ,  $\text{R}^4$ , and  $\text{R}^5$  are each independently selected from hydrogen, F, Cl,  $\text{OR}^A$ , an optionally substituted  $\text{C}_1\text{-C}_4$  alkyl, and an optionally substituted  $\text{C}_1\text{-C}_4$  haloalkyl;

wherein if  $\text{R}^1$  is  $\text{NO}_2$  and  $\text{R}^{3a}$  is F, then at least one of  $\text{R}^2$  and  $\text{R}^4$  and  $\text{R}^5$  is not hydrogen; and wherein if  $\text{R}^1$  is  $\text{NO}_2$  and  $\text{R}^3$  is F, then Z is not O;

$\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^{10}$ , and  $\text{R}^{11}$  are each independently selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl, an optionally substituted  $\text{C}_1\text{-C}_6$  haloalkyl, an optionally substituted  $\text{C}_1\text{-C}_6$  heteroalkyl, an optionally substituted  $\text{C}_2\text{-C}_6$  alkynyl, and an optionally substituted  $\text{C}_2\text{-C}_6$  alkenyl;

$\text{R}^{6a}$  and  $\text{R}^{7a}$  are each independently selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_6$  alkyl, an optionally substituted  $\text{C}_1\text{-C}_6$  haloalkyl, an optionally substituted  $\text{C}_1\text{-C}_6$  heteroalkyl, an optionally substituted  $\text{C}_2\text{-C}_6$  alkynyl, and an optionally substituted  $\text{C}_2\text{-C}_6$  alkenyl; or  $\text{R}^{6a}$  and  $\text{R}^{7a}$  together form a carbonyl;

$\text{R}^8$  and  $\text{R}^9$  are each independently selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_8$  alkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkenyl, an optionally substituted  $\text{C}_1\text{-C}_8$  haloalkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  haloalkenyl,  $\text{C}_1\text{-C}_8$  heteroalkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  heteroalkenyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkynyl, an optionally substituted  $\text{C}_2\text{-C}_8$  haloalkynyl, an optionally substituted  $\text{C}_2\text{-C}_8$  heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl,  $\text{CH}(\text{R}^D)\text{OR}^A$ ,  $\text{CH}(\text{R}^D)\text{NR}^A\text{R}^B$ , and  $(\text{CH}_2)_m\text{R}^C$ ;

$R^{12}$  and  $R^{13}$  are each independently selected from hydrogen, F, Cl,  $OR^A$ ,  $NR^A R^B$ ,  $SR^A$ , an optionally substituted  $C_1$ - $C_6$  alkyl, an optionally substituted  $C_1$ - $C_6$  haloalkyl, an optionally substituted  $C_1$ - $C_6$  heteroalkyl, an optionally substituted  $C_2$ - $C_6$  alkynyl, an optionally substituted  $C_2$ - $C_6$  alkenyl, and  $(CH_2)_m R^C$ ;

$R^{14}$  and  $R^{15}$  are each independently selected from hydrogen, F, Cl, Br, I,  $OR^A$ ,  $SR^A$ ,  $NO_2$ , CN, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, an optionally substituted  $C_1$ - $C_4$  heteroalkyl,  $NHCOR^A$ ,  $NHCONR^A R^B$ ,  $COR^A$ ,  $CO_2R^A$ ,  $CONR^A R^B$ ,  $SOR^A$ ,  $SO_2R^A$ , and  $SO_2NR^A R^B$ ;

$R^{16}$  and  $R^{17}$  are each independently selected from hydrogen, F, Cl,  $OR^A$ , an optionally substituted  $C_1$ - $C_4$  alkyl, and an optionally substituted  $C_1$ - $C_4$  haloalkyl;

$R^{18}$  and  $R^{19}$  are each independently selected from hydrogen, F, Cl, Br, I,  $OR^A$ ,  $SR^A$ ,  $NO_2$ , CN, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, an optionally substituted  $C_1$ - $C_4$  heteroalkyl,  $NHCOR^A$ ,  $NHCONR^A R^B$ ,  $COR^A$ ,  $CO_2R^A$ ,  $CONR^A R^B$ ,  $SOR^A$ ,  $SO_2R^A$ , and  $SO_2NR^A R^B$ ;

$R^{20}$  and  $R^{21}$  are each independently selected from hydrogen, F, Cl,  $OR^A$ , an optionally substituted  $C_1$ - $C_4$  alkyl, and an optionally substituted  $C_1$ - $C_4$  haloalkyl;

wherein if  $R^{18}$  is  $NO_2$  and X is O, then at least one of  $R^{19}$ ,  $R^{20}$ , and  $R^{21}$  is not hydrogen, and wherein if  $R^{19}$  is  $NO_2$  and X is C, then at least one of  $R^{18}$ ,  $R^{20}$ , and  $R^{21}$  is not hydrogen;

$R^{22}$  is selected from hydrogen, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, an optionally substituted  $C_1$ - $C_4$  heteroalkyl,

$\text{COR}^6$ ,  $\text{CO}_2\text{R}^A$ ,  $\text{CONR}^A\text{R}^B$ ,  $\text{SO}_2\text{R}^A$ , an optionally substituted aryl, an optionally substituted heteroaryl,  $\text{CH}_2\text{CH}(\text{R}^D)\text{OR}^A$ ,  $\text{CH}_2\text{CH}(\text{R}^D)\text{NR}^A\text{R}^B$ , and  $(\text{CH}_2)_m\text{R}^C$ , wherein the optionally substituted aryl or optionally substituted heteroaryl is optionally substituted with a substituent selected from F, Cl, Br, I, CN,  $\text{OR}^A$ ,  $\text{NO}_2$ ,  $\text{NR}^A\text{R}^B$ ,  $\text{SR}^A$ ,  $\text{SOR}^A$ ,  $\text{SO}_2\text{R}^A$ , an optionally substituted  $\text{C}_1\text{-C}_4$  alkyl, an optionally substituted  $\text{C}_1\text{-C}_4$  haloalkyl, and an optionally substituted  $\text{C}_1\text{-C}_4$  heteroalkyl;

$\text{R}^{23}$  and  $\text{R}^{24}$  are each independently selected from hydrogen, an optionally substituted  $\text{C}_1\text{-C}_8$  alkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkenyl, an optionally substituted  $\text{C}_1\text{-C}_8$  haloalkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  haloalkenyl, an optionally substituted  $\text{C}_1\text{-C}_8$  heteroalkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  heteroalkenyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkynyl, an optionally substituted  $\text{C}_2\text{-C}_8$  haloalkynyl, an optionally substituted  $\text{C}_2\text{-C}_8$  heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl,  $\text{CH}(\text{R}^D)\text{OR}^A$ ,  $\text{CH}(\text{R}^D)\text{NR}^A\text{R}^B$ , and  $(\text{CH}_2)_m\text{R}^C$ ; or  $\text{R}^{23}$  and  $\text{R}^{24}$  together form a carbonyl group, provided that if  $\text{R}^{18}$  is  $\text{NO}_2$  and X is NH, then  $\text{R}^{23}$  and  $\text{R}^{24}$  do not together form a carbonyl group;

$\text{R}^{22}$  and  $\text{R}^{23}$  are optionally linked to form a ring;

$\text{R}^{23}$  and  $\text{R}^{25}$  are optionally linked to form a ring;

X is selected from O, S,  $\text{CR}^A\text{R}^B$ ,  $\text{NR}^D$ , and a bond;

wherein if X is  $\text{CR}^A\text{R}^B$  or a bond, then  $\text{R}^{25}$  and  $\text{R}^{26}$  are each independently selected from a halogen,  $\text{OR}^A$ ,  $\text{NR}^A\text{R}^B$ , hydrogen, an optionally substituted  $\text{C}_1\text{-C}_8$  alkyl, an optionally substituted  $\text{C}_2\text{-C}_8$  alkenyl, an optionally substituted  $\text{C}_1\text{-C}_8$  haloalkyl, an

optionally substituted C<sub>2</sub>-C<sub>8</sub> haloalkenyl, an optionally substituted C<sub>1</sub>-C<sub>8</sub> heteroalkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> heteroalkenyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> alkynyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> haloalkynyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, and (CH<sub>2</sub>)<sub>m</sub>R<sup>C</sup>; or R<sup>25</sup> and R<sup>26</sup> together form a carbonyl group;

and wherein if X is selected from O, S, or NR<sup>D</sup>, then R<sup>25</sup> and R<sup>26</sup> are each independently selected from hydrogen, an optionally substituted C<sub>1</sub>-C<sub>8</sub> alkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> alkenyl, an optionally substituted C<sub>1</sub>-C<sub>8</sub> haloalkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> haloalkenyl, an optionally substituted C<sub>1</sub>-C<sub>8</sub> heteroalkyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> heteroalkenyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> alkynyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> haloalkynyl, an optionally substituted C<sub>2</sub>-C<sub>8</sub> heteroalkynyl, an optionally substituted aryl, an optionally substituted heteroaryl, and (CH<sub>2</sub>)<sub>m</sub>R<sup>C</sup>; or R<sup>25</sup> and R<sup>26</sup> together form a carbonyl group;

R<sup>A</sup> and R<sup>B</sup> are each independently selected from hydrogen, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, and an optionally substituted C<sub>1</sub>-C<sub>4</sub> heteroalkyl;

R<sup>C</sup> is selected from an optionally substituted aryl and an optionally substituted heteroaryl that is optionally with a substituent selected from F, Cl, Br, I, CN, OR<sup>A</sup>, NO<sub>2</sub>, NR<sup>A</sup>R<sup>B</sup>, SR<sup>A</sup>, SOR<sup>A</sup>, SO<sub>2</sub>R<sup>A</sup>, an optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, an optionally substituted C<sub>1</sub>-C<sub>4</sub> haloalkyl, and an optionally substituted C<sub>1</sub>-C<sub>4</sub> heteroalkyl;

$R^D$  is selected from hydrogen, an optionally substituted  $C_1$ - $C_4$  alkyl, an optionally substituted  $C_1$ - $C_4$  haloalkyl, and an optionally substituted  $C_1$ - $C_4$  heteroalkyl;

$Z$  is selected from O, S,  $CR^A R^B$ , and  $NR^D$ ;

$n$  is 0, 1, or 2; and

$m$  is 1 or 2;

or a pharmaceutically acceptable salt, ester, amide or prodrug thereof.

2. A compound according to claim 1, wherein the compound is selected from the group of:

$N,N'$ -bis(2,2,2-trifluoroethyl)-3-methyl-4-nitroaniline;

$N,N'$ -bis(2,2,2-trifluoroethyl)-4-nitroaniline;

5-(2,2,2-trifluoroethyl)amino-2-bromobenzotrifluoride;

4- $N,N'$ -bis(2,2,2-trifluoroethyl)amino-2-trifluoromethylbenzonitrile;

(R)-N-4-nitrophenyl-5-(dimethyl-tert-butylsilyloxymethyl)-2-pyrrolidone;

(R)-N-4-nitrophenyl-5-hydroxymethyl-2-pyrrolidone;

(R)-N-(4-nitro-3-trifluoromethylphenyl)-2-dimethyl-tert-butylsilyloxymethylpyrrolidine;

(R)-N-(4-nitro-3-trifluoromethylphenyl)-2-hydroxymethylpyrrolidine;

(R)-N-(4-nitrophenyl)-2-hydroxymethylpyrrolidine;

(R)-N-(3-Trifluoromethyl-4-nitrophenyl)-2-formylpyrrolidine;

N-(3-Trifluoromethyl-4-nitrophenyl)-2-(R)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine;

N-(3-Trifluoromethyl-4-nitrophenyl)-2-(R)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine;

(S)-N-(4-nitrophenyl)-2-hydroxymethylpyrrolidine;

N-(4-nitrophenyl)-2-(R)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine;

N-(4-nitrophenyl)-2-(R)-(1-(R)-hydroxy-2,2,2-trifluoroethyl);

N-(4-nitrophenyl)-2-(S)-(1-(S)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; and

N-(4-nitrophenyl)-2-(S)-(1-(R)-hydroxy-2,2,2-trifluoroethyl)pyrrolidine; and

pharmaceutically acceptable salts, esters, amides, and prodrugs thereof.

3. A compound according to claim 1, wherein the compound is a selective androgen receptor modulator.
4. A selective androgen receptor modulator according to claim 3, wherein the compound is an androgen receptor agonist.
5. A selective androgen receptor modulator according to claim 3, wherein the compound is an androgen receptor antagonist.

6. A selective androgen receptor modulator according to claim 3, wherein the compound is an androgen receptor partial agonist.
7. A selective androgen receptor modulator according to claim 3, wherein the compound is a tissue-specific modulator.
8. A compound according to claim 1, wherein the compound is a selective androgen binding compound.
9. A method for modulating an activity of an androgen receptor comprising contacting an androgen receptor with a compound according to claim 1.
10. The method of claim 9 wherein the androgen receptor is in a cell.
11. A method for identifying a compound that is capable of modulating an activity of an androgen receptor comprising:
  - contacting a cell expressing an androgen receptor with a compound according to claim 1; and
  - monitoring an effect of the compound upon the cell.

12. A method for treating a patient having a condition susceptible to treatment with an androgen receptor modulator comprising administering to the patient a pharmaceutical agent comprising a compound according to claim 1.
13. A method according to claim 12, wherein the patient has a condition selected from the group of acne, male-pattern baldness, wasting diseases, hirsutism, hypogonadism, osteoporoses, infertility, impotence, and cancer.
14. A method for stimulating hematopoiesis in a patient comprising administering to the patient a pharmaceutical agent comprising a compound according to claim 1.
15. A method of contraception comprising administering to patient a pharmaceutical agent comprising a compound according to claim 1.
16. A method of improving athletic performance in an athlete comprising administering to the athlete a pharmaceutical agent comprising a compound according to claim 1.
17. A pharmaceutical agent comprising a compound according to claim 1 and a pharmaceutical acceptable carrier.

18. A pharmaceutical agent according to claim 17 for use in treating a condition selected from the group of acne, male-pattern baldness, wasting diseases, hirsutism, hypogonadism, osteoporoses, infertility, impotence, and cancer.

Abstract

Disclosed herein are certain selective androgen receptor modulators and/or selective androgen binding agents. Also disclosed are methods of making and using such compounds, including, but not limited to, using such compounds for treating various conditions.